Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note

REG2003-12

Fluazinam

The active ingredient fluazinam and associated end-use product, Allegro 500F, containing the technical grade active ingredient (TGAI) fluazinam, for the control of late blight on potatoes, have been granted temporary registrations under Section 17 of the Pest Control Products (PCP) Regulations.

This Regulatory Note provides a summary of data reviewed and the rationale for the proposed regulatory decision regarding these products.

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Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has issued temporary registrations for fluazinam and the associated end-use product (EP), Allegro 500F, for the control of late blight on potatoes. This active ingredient and associated end-use product were reviewed as reduced risk pesticides under the United States Environmental Protection Agency's (USEPA) Reduced Risk Pesticides Program.

Methods for analysing fluazinam in environmental media are available to research and monitoring agencies upon request to the PMRA.

ISK Biosciences will be carrying out additional studies as a condition of these temporary registrations. Following the review of this information, the PMRA will publish a proposed registration decision document (PRDD) and request comments from interested parties before proceeding with a final regulatory decision.

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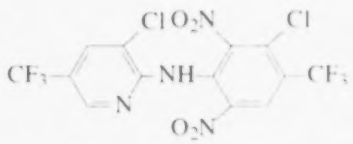
1.0 The active substance, its properties and uses

1.1 Identity of the active substance and impurities

TGAI Identification

Active substance	Fluazinam
Function	Fungicide
Chemical name	
• International Union of Pure and Applied Chemistry	3-chloro-*N*-(3-chloro-5-trifluoromethyl-2-pyridyl)-α.α.α-trifluoro-2.6-dinitro-*p*-toluidine
• Chemical Abstracts Service (CAS)	3-chloro-*N*-[3-chloro-2.6-dinitro-4-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-2-pyridinamine
CAS number	79622-59-6
Molecular formula	$C_{13}H_4Cl_2F_6N_4O_4$
Molecular weight	465.1
Structural formula	
Nominal purity of active	96.8% (nominal) (limits: 94.5–98.5%)
Identity of relevant impurities of toxicological, environmental or other significance	The technical grade fluazinam does not contain any impurities or micro contaminants known to be Toxic Substances Management Policy (TSMP) Track-1 substances. There are several toxicological issues related to one impurity, impurity no. 5 (B-1457), which is specified at 0.16% nominal with an upper certified limit of <0.3%. The data of 5 batches of TGAI were 0.07–0.28% with a mean value of 0.16 ± 0.11%.

1.2 Physical and chemical properties of active substances and end-use product(s)

Technical product: Fluazinam Technical

Property	Result	Comment
Colour and physical state	Mustard yellow solid	
Odour	Strong musty odour	
Melting point or range	Completely melted at 119°C	
Boiling point or range	Not applicable	
Density	1.76 g/cm^3	
Vapour pressure (Pa)	25°C: 2.3×10^{-5} 35°C: 1.3×10^{-4} 45°C: 6.7×10^{-5}	Low volatility
Henry's Law constant (atm m^3/mol)	pH 5: 8.11×10^{-7} pH 7: 6.73×10^{-7} pH 9: 3.11×10^{-8}	Low potential to volatilize from moist surfaces and water
Ultraviolet (UV)–visible spectrum	pH / λmax (nm) / Mean log ξ 2 / 238 / 4.31 7 / 239, 342 / 4.27, 3.86 >10 / 260, 343, 482 / 4.22, 4.27, 3.54	Some potential for phototransformation
Solubility in water at 20°C (mg/L)	pH 5: 0.131 pH 7: 0.157 pH 9: 3.384	Low solubility in basic conditions, sparingly soluble in neutral and acidic conditions.
Solubility (g/L) in organic solvents at 25°C	Solvent / Solubility (mg/mL) acetone 853 methylene chloride 675 ethyl acetate 722 ethyl ether 231 hexane 8 methanol 192 octanol 41 toluene 451	In general, solubility appears to increase with increasing organic solvent polarity.

Property	Result	Comment
Octanol–water partition coefficient (K_{ow})	Mean Log K_{ow} = 4.03 at 25°C.	Potential for bioaccumulation in biota.
Dissociation constant (pK_a)	Average pK_a = 7.22 in 50% ethanol : water (v/v)	
Stability (temperature, metal)	Thermal (TGA) tests show no evidence of degradation at up to 150°C. DSC showed no evidence of decomposition over range of 25–150°C in presence of Al, Fe and Sn powders.	

End-use product: Allegro 500F Agricultural Fungicide

Property	Result
Colour	Yellow
Odour	Pungent
Physical state	Mixture of solid powder and liquid (suspension)
Formulation type	Water dispersible granule
Guarantee	Fluazinam 40.0% (nominal), certified limits: 38.82–41.23%.
Formulants	The product does not contain any USEPA List 1 formulants or formulants known to be TSMP Track-1 substances.
Container material and description	Polyethylene jugs
Bulk density	1.259 g/mL at 25°C
pH of 1% dispersion in water	5.8 at 25°C
Oxidizing or reducing action	No oxidizing action [not reactive with $(NH_4)_3PO_4$ and Zn]. No reducing action (not reactive with 1% $KMnO_4$).
Storage stability	No change in active content (before and after storage: 41.4%, 41.5%) over 12 months at 25°C and 50% humidity.
Explodability	Not explosive

1.3 Details of uses

Allegro 500F fungicide, containing 500 g/L of fluazinam, is a contact fungicide. It is recommended for use as a preventative fungicide for control of late blight on potatoes at the rate of 200 g a.i./ha at 7–10 day intervals. A maximum of 10 applications can be applied per growing season. A maximum of three sequential applications of Allegro 500F is recommended before alternating to a fungicide with a different mode of action.

2.0 Methods of analysis

2.1 Analytical methods for analysis of the active substance as manufactured

A reversed phase HPLC/UV method was provided for the determination of the active ingredient fluazinam and the major impurities in the technical product. Based on the validation data and the chromatograms provided, the method was assessed to be sufficiently specific, precise and accurate.

2.2 Analytical methods for formulation analysis

A reversed phase HPLC/UV method was provided for simultaneous determination of fluazinam in Allegro 500F Agricultural Fungicide. Based on the validation data and the chromatograms provided, the method was assessed to be specific, precise and accurate for use as an enforcement analytical method.

2.3 Analytical methods for residue analysis

2.3.1 Methods for environmental residue analysis.

For soil, two chromatographic methods were submitted for the determination of the parent compound, fluazinam (IKF-1216) and its major transformation products, DAPA, MAPA, HYPA, CAPA and AMPA. Based on the validation data and the chromatograms provided, the methods were assessed to be sufficiently sensitive, precise, accurate and specific for the determination.

For sediment, the method used for the determination of AMPA and DAPA in soil could be used for sediments.

For water, a GC/ECD method was provided for the determination of the parent compound in runoff and surface water. Based on the validation data and chromatograms provided, the method was assessed to be sufficiently sensitive, precise, accurate and specific for the determination.

For biota, a GC/ECD method was provided for the determination of parent compound in peanut and in cow liver and muscle (loin and chuck). The method was extended to the residue method for plant matrix and animal matrices.

2.3.2 Multiresidue methods for residue analysis

The report referenced the FDA Multiresidue Protocols designated as A, C, D, E and F from PAM, Vol. I, third edition (dated January 1994). Protocol A (Section 401: Method for N-Methylcarbamates): Fluazinam (IKF-1216) was tested through Section 401 E-1 + C1 + DL1 or DL2 (HPLC/fluorescence detection). Since the test substance did not naturally fluoresce, Section 401 methodology was not further pursued. Protocol C (Gas Chromatographic Screening): Fluazinam was dissolved in iso-octane and tested using gas chromatography (GC) with electron capture (ECD) and nitrogen-phosphorus detection (NPD). Because fluazinam could be chromatographed, Section 302, 303 and 304 methods were further investigated. Protocol D (Section 302: Method I for Non-fatty Foods): Due to greater sensitivity of EC detection than N/P detection and the excellent results with Florisil observed with Protocol E (Section 303), fluazinam was tested as outlined in Section 302 E1 C1 (extraction with acetone followed by liquid/liquid partitioning; Florisil eluant 50% CH_2Cl_2/1.5% ACN/48.5% hexane). Grapes were used as the non-fatty food matrix and were spiked at 0.05 ppm and 0.5 ppm. Recoveries from grapes averaged 72.7 ± 22.0% (n = 4). Protocol E (Section 303: Method II for Non-fatty Foods): A Florisil elution test was conducted with fluazinam using three eluants each for 303/304 C1 and 303/304 C2 clean-up methodologies. The average recoveries of fluazinam from grapes using 303 C1 and 303 C2 was 114.1 ± 73.1% (n = 4) and 75.8 ± 15.3% (n = 4), respectively Protocol F (Section 304: Method for Fatty Foods): Peanut nutmeat was spiked with fluazinam at 0.05 and 0.5 ppm and analyzed as outlined in Section 304 E5 (solvent extraction of fats). The average recovery of fluazinam from peanut nutmeats using 304 C1 was 70.8 ± 8.7% (n = 4) and 86.8 ± 60.0% (n = 4) for 304 C2.

The multiresidue method (MRM) testing data indicated that fluazinam is poorly recovered through Sections 302, 303 and 304 of PAM, Vol I. Therefore, the MRM is not applicable for enforcement purposes.

2.3.3 Methods for residue analysis of plants and plant products

The residue of concern (ROC) was defined as fluazinam. The data gathering method for the analysis of fluazinam in potato matrices involved soaking samples in water prior to extraction. Fluazinam was extracted by shaking with acetic acid-methanol. An aliquot of the filtrates was acidified with 0.2N HCl and partitioned with hexane. The hexane phase was then partitioned with 0.5N NaOH and the hexane layer was discarded. The remaining aqueous phase was acidified and partitioned once again with hexane. The organic phase was concentrated by rotary evaporation and an aliquot was passed through a Florisil column. Quantitation of fluazinam was achieved by gas-liquid chromatography with electron capture detection (GLC-ECD). The method limit of quantitation (LOQ) for fluazinam was reported to be 0.01 ppm. The data gathering method was found to give acceptable recoveries [88.3 ± 6.3%] for the analysis of fluazinam in potato matrices. The standard deviations measured with respect to recoveries following spiking at the LOQ did appear to be indicative of the method having acceptable repeatability. Good linearity [correlation coefficient, r = 0.9999], was observed in the range of 0.01–1.0 μg/g for

fluazinam. Representative chromatograms of control samples of potato and processed fractions showed no interference from the matrices, reagents, solvents and glassware. The interlaboratory validation did validate the enforcement method for the residues of fluazinam, indicating good reproducibility.

2.3.4 Methods for residue analysis of food of animal origin

A data gathering and enforcement method was not presented for food of animal origin as finite residues were not expected to occur with the proposed use pattern on potatoes. However, based on the animal metabolism studies, any proposed method would have to quantify residues of fluazinam, AMPA (4-chloro-N^2-[3-chloro-5-(trifluoromethyl)-2-pyridyl]-3-nitro-5-(trifluoromethyl)-1,2-benzenediamine), DAPA ((3-chloro-2-(2,6-diamino-3-chloro-α,α,α-trifluoromethyl) pyridine) and their sulfamate conjugates.

3.0 Impact on human and animal health

3.1 Integrated toxicological summary

A detailed review of the toxicological database for fluazinam was conducted. **The database is complete, consisting of the full array of toxicity studies currently required for regulatory purposes**. The studies were carried out in accordance with currently accepted international testing protocols and good laboratory practices (GLP). **The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to this chemical.**

Fluazinam, 94.5%, was considered to be of low acute toxicity by the oral and dermal routes and of moderate toxicity by the inhalation route in SD or CD rats. It was slightly irritating when applied to the skin, but extremely irritating to eyes of New Zealand White rabbits. Results of skin sensitization testing in guinea pigs, using the Buehler method, were positive.

The formulated product, Allegro 500F, containing 40% technical, was of low acute toxicity by the oral and inhalation routes in Sprague-Dawley rats and by the dermal route in New Zealand White rabbits. It was minimally irritating when applied to the skin of New Zealand White rabbits and moderately irritating when instilled into the eyes of the same species. Results of skin sensitization testing in guinea pigs, using the Buehler method, were positive.

Absorption and excretion of single or repeated oral doses of fluazinam were rapid. A minimum of 33% of the administered dose was absorbed and excretion was almost complete, with feces as the principle route of clearance. Within 48 hours, 85–95% of the administered dose was detected in the urine and feces. Tissue residues declined rapidly, with the highest levels occurring in the gastrointestinal tract.

Metabolites AMPA, DAPA and some related conjugates and hydrolysis products were isolated, identified and characterized from urine, feces and bile of radiolabelled fluazinam-treated rats. Fluazinam was almost completely metabolized by hydroxylation, followed by conjugation. A quantitative sex difference was not observed.

A short-term dermal study showed some skin irritation after repeated applications of fluazinam to the shaved skin of albino rats. Clinical signs included decreased body weight and increased absolute and relative liver weights and hepatocellular hypertrophy.

In subchronic and chronic toxicity studies, fluazinam targeted the following organs: liver, lung, uterus, testes, pancreas, thymus, thyroid, stomach, eyes and brain. Generalized toxicity was observed in rats, mice and dogs as decreases in body weight, body-weight gain, food consumption and/or food efficiency. Liver toxicity was evident in most studies including increased size and weight, fatty changes, pallor, as well as hepatocyte hypertrophy, necrosis and apoptosis. Thyroid toxicity was less common, but included follicular hyperplasia and cystic thyroid follicles. Endocrine-related effects included small and/or flaccid testes, testicular tubular atrophy, pancreatic exocrine atrophy and thymic hyperplasia.

Long-term studies in both rats and mice provided some evidence of treatment-induced oncogenicity of the thyroid (follicular cell adenomas and adenocarcinomas) and liver (hepatocellular adenomas and carcinomas). Although tumours of this type may be the result of a non-genotoxic and non-linear mode of action, no data was provided on potential modes of action (e.g., Enzyme induction, thyroid hormone levels) There was insufficient mechanistic data to determine the mode of action. A Q^* was generated at 5.40×10^{-2} in the absence of a demonstrated mode of action.

No evidence of mutagenic potential of technical product, fluazinam, was observed in vitro with the Ames Bacterial Mutation Test. Under the conditions of an in vitro mammalian chromosomal aberration assay (cultures of Chinese hamster lung fibroblast cells), fluazinam was considered non-clastogenic. In an in vivo study, fluazinam did not induce micronuclei in a mouse micronucleus assay. In a differential growth/inhibition assay with *B. subtilis* bacteria, fluazinam was found to have no DNA-damaging potential. Based on the data presented, fluazinam was not considered to be genotoxic under the conditions of the tests performed.

There was no evidence of teratogenicity at maternally non-toxic doses in the developmental toxicity studies of rats and rabbits, however, there was evidence of qualitative sensitivity of the young. At maternally toxic doses, there were increased incidences of total litter resorptions, placental anomalies and developmental delays, variations and malformations. As in the subchronic toxicity studies, general toxicity was observed in the dams, as decreased body-weight gain and food consumption. It was teratogenic at maternally toxic doses (cleft palate, diaphragmatic hernia).

In the reproductive study, generalized toxicity was observed in parental animals, as decreases in body-weight gain and food consumption and increases in liver weight. Pups in both generations had decreased weight gain during lactation. Litter sizes were decreased in the second generation. The time to reach several developmental landmarks was decreased among F_2 pups.

In acute and subchronic neurotoxicity studies, treatment with fluazinam resulted in marked neuropathology in the form of vacuolation of the white matter of the brain. Special studies have been submitted that show this effect is not due to fluazinam itself, but rather to a manufacturing impurity. In the subchronic study, generalized toxicity was observed as decreased body weight and food efficiency. A developmental neurotoxicity study was suggested upon preliminary review of the data and the applicant submitted a rationale. Upon full review of the dataset, a developmental neurotoxicity study is a requirement for full registration.

Special studies were generated to determine the cause of the white matter vacuolation. All nine impurities were tested at doses that reflected their relative content in the technical product. Only one impurity was found to produce the vacuolation effects and all subsequent special studies focus on this chemical. The vacuolation was determined to be in the myelin sheaths surrounding axons in the white matter. Dogs, mice and rats were found to have comparable results when tested in similar manners. Older animals were found to be more susceptible than the young. All vacuolation effects were found to be reversible. Neurotoxic findings were common at high doses and included decreased motor activity, partial paralysis and ataxia. This effect was observed at high doses (LOAEL was 50 mg/kg/d) when the dose level of impurity no. 5 was sufficiently high to cause these effects. Therefore, the presence of this impurity will be limited to 0.1% of the technical active.

3.2 Determination of acceptable daily intake (ADI)

The recommended ADI for fluazinam is 0.0011 mg/kg bw/day. The chronic toxicity and oncogenicity study in mice was considered the most appropriate study to assess chronic dietary exposure. The no observed adverse effect level (NOAEL) was 1.1 mg/kg bw/day, based on increased incidences of brown pigmented macrophages in the liver, increased incidences of eosinophilic vacuolated hepatocytes in males and increased liver weights relative to body weights. The standard uncertainty factor of 100-fold is applied to account for intraspecies and interspecies variability, an additional 10-fold safety factor is recommended to firstly, protect for endocrine-related effects and secondly, to account for the lack of a developmental neurotoxicity (DNT) study. This provides margins of safety of 9100 to the NOEL for white matter vacuolation and 6350 to the NOEL for developmental effects in the rabbit developmental study.

The acceptable daily intake proposed is calculated according to the following formula:

$$ADI = \frac{NOAEL}{UF} = \frac{1.1 \text{ mg/kg bw/d}}{1000} = 0.0011 \text{ mg/kg bw/day}$$

Q* for fluazinam was calculated to be 5.4×10^{-2} based on a two-year mouse carcinogenicity study.

The USEPA has chosen an ADI of 0.00367 mg/kg bw/d based on a 2-year carcinogenicity study in mice (1.1 mg/kg bw/d with 100-fold uncertainty factor (UF) and three-fold *Food Quality Protection Act* (FQPA) safety factor.) They have also requested a developmental neurotoxicity study.

3.3 Acute Reference Dose (ARfD)

The recommended ARfD for fluazinam (general population) is 0.013 mg/kg bw. The most appropriate study for selection of a toxicity endpoint for acute dietary exposure was the rabbit developmental study, with a NOAEL of 4 mg/kg bw/day, based on decreased food consumption and liver histopathology at 7 mg/kg bw/day. The standard uncertainty factor of 100-fold is applied to account for intraspecies and interspecies variability and an additional 3-fold safety factor is recommended to protect for sensitivity of the young.

$$\text{ARfD (general population)} = \frac{NOAEL}{UF} = \frac{4 \text{ mg/kg bw}}{300} = 0.013 \text{ mg/kg bw}$$

The USEPA has chosen an ARfD of 0.167 mg/kg bw based on an acute neurotoxicity study in rats (50 mg/kg bw with 100-fold UF and three-fold FQPA safety factor.)

The recommended ARfD for fluazinam (females 13+) is 0.007 mg/kg bw. The most appropriate study for selection of a toxicity endpoint for acute dietary exposure was the rabbit developmental study, with a developmental NOAEL of 7 mg/kg bw/day, based on total litter resorptions, placental anomalies and developmental delays, variations and malformations in the fetuses at 12 mg/kg bw/day. The standard uncertainty factor of 100-fold is applied to account for intraspecies and interspecies variability, an additional 10-fold safety factor is recommended firstly, to protect for sensitivity of the young and secondly, to account for the lack of a developmental neurotoxicity (DNT) study.

$$\text{ARfD (females 13+)} = \frac{NOAEL}{UF} = \frac{7 \text{ mg/kg bw}}{1000} = 0.007 \text{ mg/kg bw}$$

The USEPA has chosen an ARfD of 0.007 mg/kg bw based on a rabbit developmental study in rabbits (7 mg/kg bw with 100-fold UF and 10-fold FQPA safety factor.)

3.4 Toxicological endpoint selection: occupational and bystander risk assessment

Occupational exposure is characterized as short-term or intermediate and is predominately by the dermal route. There was a 21-day repeat dose dermal toxicity study available, however, it does not account for the treatment-related histopathological and reproductive endpoints noted in rats and rabbits following 90-day and 1-year dietary administration. It is recommended that the rabbit developmental study with a NOAEL of 4 mg/kg bw/d be used for short-term exposure scenarios and the rat two-generation reproduction study with a NOAEL of 1.9 mg/kg bw/d be used for intermediate-term exposure scenarios. A margin of exposure (MOE) of 300 is recommended based on 100-fold to account for intraspecies and interspecies difference and an additional three-fold to account for a lack of a developmental neurotoxicity study.

Long-term studies in both rats and mice provided some evidence of treatment-induced oncogenicity of the thyroid (follicular cell adenomas and adenocarcinomas) and liver (hepatocellular adenomas and carcinomas). Although tumours of this type may be the result of a non-genotoxic and non-linear mode of action, no data was provided on potential modes of action (e.g., enzyme induction, thyroid hormone levels). There was insufficient mechanistic data to determine the mode of action. A Q* was generated at 5.40×10^{-2} in the absence of a demonstrated mode of action.

Dermal absorption

Since the short-term and intermediate-term NOAELs and Q* value are based on oral toxicology studies, systemic exposure will be calculated from dermal deposition estimates using a 9% dermal absorption value. This value is based on a chemical-specific in vivo dermal absorption study entitled, *Dermal Absorption of [^{14}C]-Fluazinam in Two Formulations in the Rat*.

Male Sprague Dawley rats were treated with [^{14}C]-fluazinam at nominal doses of 5 and 5000 μg a.i./cm^2. All rats were exposed for 6 hours and sacrificed at 6, 24 and 48 hours. Protective devices (Lomir rat jacket, gauze and O-ring), skin wash, cage wash, urine, feces, skin test site, tape strips from skin test site, carcass, GI tract, liver, whole blood and plasma were analysed for radioactivity. Recovery of the applied dose was acceptable (95.05 to 108.41%). The majority of the administered dose was recovered from the skin wash (82.29 to 99.79%).

Limitations noted in the review of the study include insufficient exposure groups, a short exposure duration and the use of Swarfega® for the skin wash. Exposure durations for handlers and re-entry workers are expected to fall between 8 and 12 hours. Dermal absorption trends that may occur with increasing exposure durations could not be assessed as there was only one exposure duration of 6 hours. With respect to the skin wash, Swarfega®, an industrial cleaning gel, may not be representative of normal hygiene practices.

A dermal absorption value of 9% selected from the low-dose, 48 h sacrifice group based on the sum of whole blood, plasma, GI tract, liver, carcass, urine, feces, skin test site, tape strips and cage wash, will be used for risk assessment purposes. This dermal absorption value is not considered to be conservative given the limitations of the study.

3.5 Impact on human and animal health arising from exposure to the active substance or to impurities contained in it

3.5.1 Operator exposure assessment

Allegro 500F Agricultural Fungicide is formulated as a suspension (500 g a.i. per litre) and will be used on potatoes to control late blight. The label allows application by ground only. Therefore, application would be by standard groundboom equipment. Farmers or custom applicators may mix, load and apply to potatoes. Typical mean hectarages treated per day for growers/farmers and custom applicators are 65 ha and 300 ha, respectively. The application rate of Allegro 500F Agricultural Fungicide is 200 g a.i./ha with up to 10 applications permitted per season at 7- to 10-day intervals. Therefore, it is expected that farmers could apply a maximum of 13 kg a.i./day and custom applicators could apply a maximum of 60 kg a.i./day.

It is expected that farmers may be exposed up to 25 days per season (10 days application, up to 15 scouting events) and custom applicators may be exposed daily per season. Exposure is expected to be predominately by the dermal route. Therefore, exposure to farmers and custom applicators or professional potato scouts is expected to be intermittent short-term and intermittent intermediate-term in duration, respectively.

Exposure assessment

Pesticide Handlers Exposure Database (PHED Version 1.1) assessments were conducted to derive estimates of occupational exposure for mixers/loaders and applicators. The data were based on high confidence PHED runs, adequate numbers of replicates and A+B grade data except for the groundboom applicator, closed cab scenario where A+B+C grade data were used. The PHED estimates generated generally conform with NAFTA Guidelines for using and reporting PHED data. PHED data do not provide exposure estimates for clean-up/repair activities nor quantify the variability of exposure estimates. Exposure via the inhalation route was a minor component of overall exposure. Total systemic exposure was determined by summing dermal deposition estimates (adjusted for dermal absorption) and inhalation estimates.

Exposure estimates are presented on the basis of the best-fit measure of central tendency, i.e., summing the measure of central tendency for each body part which is most appropriate to the distribution of data for that body part. Exposure estimates for open mixing and loading of Allegro 500F Agricultural Fungicide were derived for individuals wearing a single layer of clothing (long-sleeved shirt and long pants) and gloves. For groundboom applicators, estimates were derived for individuals wearing a single layer of clothing and no gloves. For custom groundboom application, exposure estimates were

derived for a closed cab scenario. Exposure estimates and margins of exposure derived for mixer/loader/applicators are presented in Table 3.5.1.1.

Table 3.5.1.1 Mixer/loader/applicator exposure

Occupational scenario	Exposure [1] (mg/kg bw/day)	Margin of exposure [2]
Mixer/loader + groundboom application (grower/farmer)	0.001881	2127
Mixer/loader + groundboom application (custom)	0.00622	305

1 Based on mixers/loaders wearing a single layer and gloves and groundboom applicators wearing a single layer and no gloves. Exposure refers to the sum of dermal deposition and inhalation estimates. Dermal deposition estimates were adjusted for a 9% dermal absorption value. For custom application, a closed cab scenario was used and for application by farmers, an open cab scenario was used.

2 For growers/farmers (short-term exposure), the maternal NOAEL of 4 mg/kg bw/day from the rabbit developmental study was used, target MOE of 300. For custom applicators (intermediate exposure), a NOAEL of 1.9 mg/kg bw/day from the multi-generation reproductive/developmental toxicity study was used, target MOE of 300.

These margins of exposure are acceptable.

A cancer assessment was also conducted for mixer/loader/applicators of fluazinam and are presented in Table in 3.5.1.2.

Table 3.5.1.2 Mixer/loader/applicator cancer risk assessment

Occupational scenario	Daily exposure estimate (mg/kg bw/day)[1]	LADD (mg/kg bw/day)[2]	Cancer risk (based on a Q* of 0.054 mg/kg bw/day^{-1})[3]
Growers/ Farmers	0.001881	2.75×10^{-5}	1.48×10^{-6}
Custom Applicator	0.00622	5.00×10^{-4}	2.70×10^{-5}

1 Daily exposure based on farmers and custom applicators wearing a single layer and gloves, open mixing and loading of Allegro 500F Agricultural Fungicide and custom applicators using a closed cab for groundboom application

2 LADD was calculated using the following formula:

$$\frac{\text{Daily exposure estimate (mg/kg bw/day)} \times \text{frequency (days/year)} \times \text{duration (40 years/lifetime)}}{\text{Lifetime (75 years)} \times \text{Conversion Factor (365 days/year)}}$$

It was assumed that farmers would be exposed for 10 days per year and custom applicators would be exposed for 55 days per year

3 Cancer risk calculated using the following formula: LADD × Q*

The acceptability level for cancer risk is one in a million (1×10^{-6}). Risk levels between 1×10^{-5} to 1×10^{-6} may trigger the need for risk mitigation. A cancer risk of 1.48×10^{-6} for farmers is considered to be acceptable. The cancer risk of 2.70×10^{-5} for custom applicators is considered to be acceptable given the following conservatisms in the risk assessment: the use of a high-end area treated per day (300 ha/day), the assumption that custom applicators perform both the mixing and loading and application of pesticides and the assumption that custom applicators would be exposed for 55 days per year for 40 years of their lives. Although the expected exposure duration is difficult to anticipate, it is unlikely that custom applicators would be exposed to the same product 55 days per year for 40 years of their lives.

However, to mitigate any potential risk to custom applicators, coveralls over a single layer of clothing will be required during mixing, loading and application.

3.5.2 Bystanders

For the proposed agricultural use scenario, bystander exposure during and after application was considered minimal compared to mixer/loader/applicator and re-entry worker scenarios and, therefore, not quantified.

However, to promote best management practices and to minimize human exposure from spray drift or from spray residues resulting from drift, the following label statement that emphasizes the importance of minimizing drift will be incorporated into the final label:

> *"Apply only when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature, application equipment and sprayer settings."*

3.5.3 Workers

Post-application exposure is expected for workers re-entering treated potato fields to perform scouting. Growers/farmers typically scout their own potato fields once a week (approx. 1 h in duration), however, there are professional potato scouts who may scout potato fields for up to 4 hours per day all season long.

The primary route of exposure to potato scouts is dermal through contact with treated foliage. Professional potato scouts may be exposed daily throughout the season, therefore exposure is expected to be intermittent intermediate-term in duration.

To assess post-application exposure, the applicant submitted a chemical-specific dislodgeable foliar residue (DFR) study conducted on potatoes. The DFR study was unacceptable for use quantitatively in the exposure assessment as the analytical method used to quantify fluazinam residues was considered inadequate (lab recovery ranged from 40 to 114%, n=18, SD ± 24). However, the results from the study support increasing the standard default of 10% dissipation per day to 20% dissipation per day.

To estimate exposure to scouts re-entering treated potato fields, it was assumed that 20% of the application rate was dislodgeable on the day of application and that workers would spend 4 hours per day scouting treated potato fields. The Agricultural Re-entry Task Force (ARTF) transfer coefficient of 1500 cm^2/h (the applicant, ISK Biosciences, is a member of ARTF) was used in the calculation of exposure estimates. It was assumed that dislodgeable foliar residues were cumulative with each successive application.

The highest daily exposure of 0.00388 mg/kg bw/day, obtained on the day of the 6^{th} application, was compared to the short-term NOAEL of 4 mg/kg bw/day to obtain an acceptable MOE of 1031 (>300). In addition, an average seasonal exposure, calculated from summing the expected daily exposures for the season and dividing by the number of days in the season, of 0.001455 mg/kg bw/day resulted in a MOE of 1306. This MOE is based on the intermediate-term NOAEL of 1.9 mg/kg bw/day from the multi-generation reproductive/developmental toxicity study. This MOE is considered to be acceptable (>300).

A cancer assessment was conducted for potato scouts by calculating a lifetime average daily dose and multiplying it by the Q^* of 0.054 mg/kg bw/day^{-1}. Assuming a 24 hour re-entry interval, the lifetime average daily dose of 1.78×10^{-4} mg/kg bw/day was calculated by multiplying the seasonal exposure by duration of exposure (assumed to be a 40 year working career) divided by the average lifespan (assumed to be 75 years) and the number of days per year (365 days/year). The calculated cancer risk of 9.62×10^{-6} is considered to be acceptable.

4.0 Residues

4.1 Residue summary

Nature of the residue in potato plants

Fluazinam (radiolabelled in the phenyl or pyridine rings) was applied foliarly four times to potato plants, at the rate of 0.505 kg a.i./ha nitrophenyl (PH) for a total of 2.02 kg a.i./ha, or 0.430 kg a.i./ha pyridine (PY) for a total of 1.72 kg a.i./ha (0.85 to one-fold). The initial application was at the flowering and tuber formation stage (72 days after planting) and subsequent applications were executed at 86, 97 and 106 days after planting. In whole potatoes, the largest fraction of the radioactivity from both labels (>40% of the total radioactive residues (TRRs)) was incorporated into starch (4.87 to 11.83 ppb). A mixture of polar metabolites resulting from extensive degradation of the parent compound was also a major component of the total radioactive residues (>25% of

the TRRs). The parent compound, fluazinam, and the metabolites AMGT (3-[[4-amino-3-[[3-chloro-5-(trifluoromethyl)-2-pyridinyl]amino]-2-nitro-6-(trifluoromethyl)phenyl]thio]-2-(β-D-glucopyranosyloxy) propionic acid) and AMPA (4-chloro-N^2-[3-chloro-5-(trifluoromethyl)-2-pyridyl]-3-nitro-5-(trifluoromethyl)-1,2-benzenediamine) were present at less than 10% of the TRRs (0.16 to 1.46 ppb). Fluazinam residues from the PY label were found predominantly in the potato peel (1.6 ppb), compared with residue in the pulp (0.1 ppb). The metabolic pathway of fluazinam involves reduction of one or both nitro groups to form AMPA or DAPA ((3-chloro-2-(2,6-diamino-3-chloro-α,α,α-trifluoromethyl) pyridine), replacement of the phenyl ring chlorine by glutathione conjugation and then further metabolism/conjugation. Also, the end products of metabolism involve re-incorporation of ^{14}C from fluazinam into natural products, including starch. The residue of concern (ROC) may be defined as fluazinam.

Confined/field accumulation in rotational crops

The confined crop rotational study was conducted by application of ^{14}C-nitrophenyl-fluazinam or 2,6-^{14}C-pyridine-fluazinam twice to sandy loam soil at a rate of 1.12 kg a.i./ha, for a total of 2.24 kg a.i./ha. Each plot was divided into three crop sections for the rotational crops (barley, carrots and lettuce) to be planted at 30, 120 and 365 days after treatment (DAT). Characterization and identification of the major components in extracts was achieved using a variety of methods including fluorine nuclear magnetic resonance (NMR), derivatization and liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) analysis. The analyses indicated that extensive metabolism on the pyridine substituent had occurred. Fluorine NMR showed that there was no longer an aromatic trifluoromethyl group. MS/MS analysis of the acetylated unknown indicated two components that did not contain chlorine, and appeared to be from fragments retaining only two carbons of the pyridine ring. These results show that extensive metabolism, ring opening and fragmentation had also occurred with the pyridine ring. Characterization of the non-extractable residue from the 30-DAT barley grain demonstrated that ^{14}C residues from fragmentation of the pyridine ring had been reincorporated into natural product carbohydrates. The analytical reference standards used in the study included parent, AMPA, MAPA, DAPA (all three represent reduction of one or both nitro groups), HYPA (displacement of phenyl chlorine by hydroxyl), CAPA (oxidation of pyridinyl CF_3 group to COOH) and trifluoroacetic acid (TFA). The organic fraction of each crop matrix contained less than 10% (or less than 0.01 ppm) of the TRRs. Metabolites containing the intact fluazinam nucleus were expected to be found in that fraction. Radioactivity in the aqueous fractions accounted for up to 75–95% of the TRRs (0.06–0.27 ppm) in nitrophenyl-labelled crops, and up to 27–60% of the TRRs (0.02–0.046 ppm) in pyridine-labelled crops. Trifluoroacetic acid (TFA) was identified as the major residue in crops with significant aqueous extractable residues. The TRRs values for the edible (i.e., human food) commodities ranged from 0.034–0.282 ppm for lettuce, <0.010–0.070 ppm for carrot roots and 0.054–0.296 ppm for barley grain at various plant-back intervals. **No residues of fluazinam or any metabolite with the intact fluazinam nucleus were found in any of the rotational crops.** The data support a rotational crop restriction of 30 days for root crops and leafy vegetables and 70 days for small cereal grains (except for potatoes, which can be planted at any time).

Nature of the residue in animals

Fluazinam, radiolabelled in the PH or PY rings, was administered orally to white leghorn laying hens and lactating goats at a dose level equivalent to approximately 10 mg/kg feed per day for 4 consecutive days. The main route of elimination of radioactivity was via the feces. The predominant residues from both labels in goat were the reduction products AMPA (3.7 to 50.9% of TRRs) in liver (PY only), kidney, muscle, fat and milk (up to 0.126 ppm in fat (PY)), DAPA (2.1 to 49.2% of TRRs) in liver, kidney, muscle, fat, milk, urine and bile (up to 0.43 ppm in bile (PY)) and sulfamate conjugates of AMPA and DAPA (1.5 to 85% of TRRs) in milk, urine, bile, liver and kidney (up to 3.94 ppm in bile (PH)). The predominant residue in poultry tissues and eggs, with more than 10% of the TRRs, was AMPA (0.017 to 0.767 ppm). Minor residues (<10% of the TRRs) were fluazinam, MAPA (3-chloro-*N*^{1}-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]-6-nitro-4-(trifluoromethyl)-1,2-benzenediamine), DAPA, and HYPA (5-[(3-chloro-5-(trifluoromethyl)-2-pyridyl)amino]-α,α,α-trifluoro-4,6-dinitro-o-cresol).

The metabolism of [^{14}C]-fluazinam in ruminants and poultry is similar and involves reduction of one or both nitro groups on the phenyl ring to form the mono- and di-amino metabolites, AMPA, MAPA and DAPA. Fluazinam also undergoes dehalogenation and hydroxylation of the chlorine on the phenyl ring to form HYPA. These compounds may then undergo conjugation with glutathione and subsequent degradation of the glutathione component yielding a variety of polar compounds. Although the ring structure of the parent molecule remains intact, fluazinam was only a minor component (<2.7% of the TRRs) of the ^{14}C-residues in poultry tissues and eggs and was not detected in ruminant tissues or milk. The metabolic profiles of goats and hens are similar to that of rat. Therefore, the residue of concern (ROC) in animal products may be defined as fluazinam, AMPA, DAPA and their sulfamate conjugates. The metabolism of fluazinam in animals is adequately documented.

Methods for residue analysis of plants and plant products

A method using gas-liquid chromatography with electron capture detection (GLC/ECD) was proposed for data gathering purposes. The method for enforcement is essentially the same as the data gathering method with some minor modifications to improve the extraction of analytes in the various matrices. The method limit of quantitation (LOQ) for fluazinam was reported as 0.01 ppm. Representative chromatograms of control samples of potato and processed fractions did not indicate interferences from the matrices or reagents. This method was found to give acceptable recoveries (88.3±6.3%) for the analysis of fluazinam in potato matrices. The interlaboratory validation did support the reliability and reproducibility of the method for the determination of the fluazinam in potato matrices. The method has been adequately radiovalidated. The multiresidue method testing data indicated that fluazinam is poorly recovered through Sections 302, 303 and 304 of PAM, Vol I., with recoveries being dependent on which Florisil elution system was used. Therefore, the MRM is not applicable as an enforcement method for residues of fluazinam.

Methods for residue analysis of food of animal origin
A data gathering and enforcement method was not presented for food of animal origin as finite residues were not expected with the proposed use pattern on potatoes. However, based on the animal metabolism studies, the method would have to quantify residues of fluazinam, AMPA, DAPA and their sulfamate conjugates since they were identified in animal matrices.

Storage stability data—potatoes
Samples of whole potatoes and processed potato matrices (chips, granules, wet peel) were homogenized and spiked with fluazinam at a level of 0.5 ppm and stored at -20°C for up to 1149 days. At each of the sampling intervals, four replicates spiked (stored) samples were analysed along one control sample and two concurrent (fresh) spiked samples. Under these conditions, fluazinam levels decreased by 40% in wet peels; 43% in whole potatoes; 23% in potato chips; and 70% in potato granules. The data presented in the freezer storage stability study indicated that residues of fluazinam degraded at -20°C but were still recoverable (78–90%) after 363 days in whole potatoes, 1149 days in potato chips, 182 days in wet peels and 57 days in potato granules. This information will be considered in adjusting the residue trial data.

Crop field trials
A total of 19 supervised crop field trials in potato tubers were conducted from 1992 to 1994 in Canada and U.S. Zones 1 (7 trials), 1A (1 trial), 5 (2 trials), 5A (2 trials), 9 (2 trials), 10 (2 trials) and 11 (3 trials). Although trials were under-represented in Canada's growing region (1A, 5B, 7A, 12, 14), the consistency of residues below the LOQ in all sites will be weighed in addressing this deficiency. Plants were treated foliarly with Allegro 500F (Fluazinam 40% w/w) 2 to 11 times with 6 to 27 day intervals, at 0.2 to 0.5 kg a.i./ha, for a total application rate of 1.0 to 2.3 kg a.i./ha. [0.5-fold to 1.1-fold the proposed maximum label rate]. The fluazinam residues in potato tubers collected 8, 14, 18, 32 and 40 days after the last application were all less than the reported LOQ of 0.01 ppm. Therefore, the proposed PHI of 14 days can be supported.

Processed food/feed
Allegro 500F [Fluazinam 40% w/w] was applied to potatoes at a maximum rate of 5.7 kg a.i./ha (2.9-fold the recommended application rate) and the potatoes were processed into dry peels, wet peels, flakes, granules, french fries and chips. A comparison of the residues in the raw agricultural commodity (RAC) with those in each processed fraction resulted in no apparent concentration (all levels were below the LOQ). Additional MRLs are not required to cover residues of fluazinam in processed potato fractions.

Meat/milk/poultry/eggs
Assuming maximum residue limits for fluazinam residues in/on animal feed items (potato, peanut), the calculated maximum theoretical dietary burden for livestock is 0.05 ppm for beef and dairy cattle. Based on this maximum dietary exposure, the 11 ppm dose level used in the ruminant metabolism study reflects 220-fold the dose level. Based on the nature of the residue study in goat, the residues of concern in livestock

commodities are parent plus the metabolites AMPA, DAPA and their sulfamate conjugates. In the animal metabolism studies, residues of fluazinam were not detected in dairy goat milk or tissues. The maximum levels of the metabolites of concern from the goat metabolism study were 0.224 ppm (liver); 0.027 ppm (kidney); 0.02 ppm (muscle); 0.204 ppm (fat) and 0.058 ppm (milk). Extrapolating these values to the maximum expected cattle burden, both total DAPA and total AMPA anticipated residues would be less than 1 ppb (0.001 ppm) in milk, fat and tissues. Based upon the above results, feeding studies and maximum residue limits for livestock commodities are not required. If significantly higher dietary burdens are encountered in the future, such studies would probably be required.

Dietary risk assessment

Chronic dietary exposure analyses were performed in order to determine the exposure and risk estimates which result from the use of fluazinam on potatoes in Canada, including peanuts imported into Canada. The assessment used the maximum residues limits and assumed 100% crop treated. Risk estimates for the representative population subgroups ranged from 1.2% to 3.9% of the ADI. The analysis showed that dietary risk estimates were below the level of concern (100% of the ADI) for the general population and all population subgroups. The acute dietary exposure for females 13+ (ARfD = 0.007 mg/kg bw) was estimated at 1.0% from all supported fluazinam food uses and 0.6% for the total population (ARfD = 0.013 mg/kg bw). The currently proposed use for fluazinam encompassed only agricultural use sites. Therefore, when addressing aggregate exposures, only the dietary pathways of food and drinking water were considered. Acute and chronic aggregate exposures were considered acceptable and did not exceed the level of concern. A lifetime cancer risk (Q*) was conducted as a conservative linear low dose extrapolation to determine the cancer risk. The lifetime cancer risk (Q* = 0.054 mg/kg bw) from dietary exposure to fluazinam was estimated to be in the range of 7.4×10^{-7} to 1.2×10^{-6} for food alone, and 1.2×10^{-6} to 3.2×10^{-6} for food and water within all population subgroups. Although the lifetime cancer risk values slightly exceed our cancer risk assessment threshold (1×10^{-6}), the cancer risk for both food and water was considered acceptable, in the absence of mechanistic data to demonstrate a probable threshold cancer effect. Mechanistic data has been requested by toxicology.

5.0 Fate and behaviour in the environment

The fate and behaviour in the environment is summarized in Table 7.

5.1 Physical and chemical properties relevant to the environment

Fluazinam was determined to be of sparing to low solubility in water depending on the pH (pH 5: 0.13 mg/L; pH 7: 0.157 mg/L; pH 9: 3.38 mg/L). The vapour pressure of fluazinam at 25°C indicates that the compound would be of low volatility (2.3×10^{-5} Pa). The Henry's Law constant of fluazinam indicates that the chemical will have low potential to volatilize from water and moist surfaces (pH 5: 8.11×10^{-7} m^3/mol; pH 7: 6.73×10^{-7} m^3/mol; pH 9: 3.11×10^{-8} m^3/mol). The magnitude of the octanol–water

partition coefficient for fluazinam indicates that there is a potential for bioaccumulation (K_{ow} 4.03). The dissociation constant, pK_a, of the compound indicates it dissociates under acidic and basic conditions (7.22). The UV–visible absorption spectrum of fluazinam indicates that the compound has potential to phototransform at environmentally relevant wavelengths of light (pH 7= λ: 342 nm, pH >10= λ: 343, 482 nm).

5.2 Abiotic transformation

Fluazinam was stable to hydrolysis at pH 5 at 22°C, but hydrolyzed at pH 7 and 9 with half-lives of 42 and 5.6 days, respectively. One major hydrolytic transformation product, CAPA, was formed at pH 7 and 9. The phototransformation half-life of fluazinam on a sandy loam soil at 25°C was 22.2 days, with no major transformation products formed. Phototransformation of fluazinam in a sterile pH 5 aqueous solution at 25°C was rapid with a half-life of 2.5 days. The half-life of photolysis studies were greater than 7 days in soil. Abiotic transformation, therefore, will be an important route of transformation in water.

5.3 Biotransformation

Results of biotransformation studies with fluazinam in a sandy loam soil under aerobic conditions at 20°C and 1 kg/ha application rate yielded half-lives of 72 and 38 days for phenyl and pyridyl radiolabels, respectively, with no major transformation products formed. The sandy loam soil at 5 kg/ha application rate yielded half-lives of 120 and 150 days, respectively, with the formation of the major transformation product, HYPA. The sandy loam soil at 10°C and 1 kg/ha yielded half-lives for both radiolabels of 200 and 160 days, respectively, with no major transformation products formed. Results with a loamy sand soil under aerobic conditions at 20°C and 1 kg/ha application rate yielded half-lives of 200 and 152 days, respectively, with no major transformation products formed.

Results of biotransformation studies with fluazinam in the sandy loam soil under anaerobic conditions with no aerobic pre-incubation at 20°C and 1 kg/ha application rate yielded half-lives of 4.5 days for both radiolabels, with the formation of major transformation products, MAPA and DAPA. The same soil with a 30-day pre-incubation prior to anaerobic conditions yielded half-lives of 32 days, and formation of the major transformation product, HYPA. All transformation products reached maximum concentrations and declined to <1% by test termination (day 183). These results indicate that fluazinam will be slightly persistent to persistent in aerobic soil according to the classification system of Goring et al. (1975). Under environmentally relevant conditions, fluazinam will be slightly persistent in anaerobic soil.

Results of biotransformation studies in an aerobic water-sediment system (9:1 water to loamy sand sediment ratio) from Ohio at 25°C yielded half-lives of 20 and 32 hours with phenyl and pyridyl radiolabels, respectively, with the formation of several major transformation products, DCPA, CAPA, DAPA and AMPA. A second aerobic water-

sediment system (2.5:1 water to sediment) with a loamy sand and sandy loam sediment at 25°C yielded half-lives of 2.9 and 3.2 days with the phenyl and pyridyl radiolabels, respectively, with formation of major transformation products, DAPA and AMPA in the loamy sand sediment and AMPA in the sandy loam sediment. The half-life of fluazinam in an anaerobic water-sediment system 25°C (7.5:1 water to sand sediment) was less than one day in both radiolabels, with the formation of major transformation products, DAPA, AMPA, SDS-67200 and unidentified radioactivity which accounted for up to 67% of the material balance. These results indicated that fluazinam will be non-persistent in aerobic and anaerobic aquatic systems according to the classification scheme of McEwan and Stephenson (1979). All transformation products declined by test termination (day 30), except DAPA which was present up to 19% by day 30.

5.4 Mobility

The adsorption K_d and K_{oc} values for fluazinam in four soils (sand, loamy sand, silt loam and clay) ranged from 11 to 43 mL/g and from 1705 to 2316 mL/g, respectively. The adsorption K_d and K_{oc} values for the transformation product, HYPA, in six soils (one loamy sand, three sandy loams, one coarse sand and one silty clay loam) ranged from 4.3 to 26 mL/g and 450 to 1667 mL/g, respectively. The adsorption K_d and K_{oc} values for the transformation product, CAPA, in four soils (silty loam, loamy sand, sandy loam and silty clay) ranged from 5 to 67 mL/g and 1284 to 3784 mL/g, respectively. These results indicate that based on K_{oc} values, fluazinam will be of slight mobility in sand soils, and of low mobility in loamy sand, silty loam and clay soils. Based on adsorption K_{oc} values, HYPA will be of low to slight mobility in sandy loam soils, and low mobility in silty clay loam, loamy sand and sandy loam soils, and of moderate mobility in coarse sand soils; and CAPA will be of low mobility in silty loam, loamy sand and sandy loam soils, and of slight mobility in silty clay soils, based on the classification system of Goring et al. (1975). Results from the 'aged soil' leaching study indicated that less than 5% of phenyl and pyridyl radioactivity was present at >10 cm of soil depth in both the sandy loam and loamy sand soils. Based on the values for vapour pressure and Henry's Law constant, fluazinam has low volatility with low potential for volatilization under alkaline conditions.

5.5 Dissipation and accumulation under field conditions

Results of terrestrial field studies of dissipation and accumulation conducted in Canada (Ecoregions 5.1 and 5.2) indicated that fluazinam was moderately persistent in soil, with DT_{50} values of 81.5 and 95 days with significant carryover (up to 52%) of residues to the next season. The major transformation product HYPA was formed at all Canadian and American study sites. HYPA showed a trend of increasing concentrations in soil towards the end of the study (day 270) at one Canadian site, reaching 8% of fluazinam. At the other Canadian site, HYPA remained stable between days 0 and 99, representing 3–6% of fluazinam residues, and increased on day 268, where it remained 12–15% of fluazinam residues until termination of the study (day 367). There was no evidence of leaching of fluazinam or HYPA through the soil layers. Field dissipation studies conducted in the

United States (Ecoregions 9.2 and 6.2) yielded DT_{50} values of 19 and 33 days, respectively. The transformation product, HYPA, showed a trend of decreasing concentrations in soil towards the end of the study at one of the U.S. sites, reaching 5.8% of fluazinam. At one of the U.S. sites, HYPA reached 15% on day 7 and declined to only 0.9% by day 357. Although analyses of CAPA and MAPA were not included in the Canadian field studies, these transformation products are not expected to amount to concentrations greater than 10% based on field and laboratory data.

5.6 Bioaccumulation

Bluegill sunfish (*Lepomis macrochirus*) were exposed to phenyl and pyridyl [^{14}C] ring-labelled fluazinam in a bioconcentration study consisting of an uptake (exposure) phase of 35 days and a depuration phase of 21 days. At the end of the uptake phase, average tissue concentrations of ^{14}C-fluazinam in both radiolabels ranged from 3.9 to 230 µg/kg for fillet, 39 to 790 µg/kg for whole fish, and from 56 to 1200 µg/kg for viscera. The daily bioconcentration factors (BCFs) in both radiolabels ranged from 5.8 to 348, 58 to 1220, and 84 to 1850 for fillet, whole fish and viscera, respectively. At the end of the 21- day depuration phase, approximately 67 to 81% of both radiolabelled fluazinam was eliminated from fillet, whole fish and viscera, respectively. Based on whole fish data, the uptake rate constant (K_1) values were 114 to 117 µg/kg fish/µg/L water/day for both radiolabels, and the corresponding depuration rate constant (for 50% depuration) (K_2) values were 0.11 to 0.14; the bioconcentration factors were 827 to 1018, and the time to reach 90% of steady state was 17 to 20 days in both radiolabels. No major metabolites were formed throughout the study. Minor transformation products, AMPA, MAPA, DAPA and UK-1 (unidentified metabolite), reached ≤5% at test termination in both fillet and viscera. At days 28 and 35 of the study, fluazinam accounted for ≤ 1.7% in both viscera and fillet tissue. It is concluded that fluazinam is readily taken up by bluegill sunfish (K_{ow}: 4.03) resulting in a BCF ranging from 827 to 1018, most of which is excreted as the parent compound. Up to 50% of the parent compound is depurated within 5 to 6 days.

5.7 Summary of fate and behaviour in the terrestrial environment

Fluazinam was determined to be of sparing to low solubility in water, which is one of the indicators of low potential for leaching. The vapour pressure and Henry's Law constant of fluazinam indicates that the compound would be considered of low volatility. The UV–visible absorption spectrum of fluazinam indicates that the compound has potential to phototransform at environmentally relevant wavelengths of light, however the phototransformation half-life of fluazinam on soil was 22.2 days, with no major transformation products formed, indicating that it will not be an important route of transformation in soil. Hydrolysis is expected to be an important route of transformation under alkaline conditions, with formation of the major transformation product, CAPA.

Results of aerobic soil biotransformation studies with fluazinam in a sandy loam soil at varying application rates and temperatures (20°C and 1 kg/ha half-life: 38–72 days; 20°C

and 5 kg/ha half-life: 120 to 150 days; 10°C and 1 kg/ha: 160–200 days, for both radiolabels) and a loamy sand (20°C and 1 kg/ha half-life: 162–200 days) indicates that fluazinam will be slightly persistent to persistent (Goring et al. 1975). The transient major transformation product, HYPA, was formed in the sandy loam soil at 5 kg/ha and 20°C.

Results of anaerobic soil biotransformation studies with fluazinam in a sandy loam soil under anaerobic conditions (half-life: 4.5 days for both radiolabels) and aerobic pre-incubation (half-life: 32 days for both radiolabels) indicate that fluazinam will be non-persistent to slightly persistent (Goring et al. 1975). The formation of transient major transformation products, HYPA, MAPA and DAPA were formed.

The adsorption K_{oc} values for fluazinam (1705 to 2316 mL/g), HYPA (450 to 1667 mL/g) and CAPA (1289 to 3784 mL/g) in varying soil types (sand, loamy sand, silt loam and clay soils) indicate that fluazinam will be of slight mobility in sand soils and of low mobility in loamy sand, silty loam and clay soils; HYPA will be of low to slight mobility in sandy loam soils and low mobility in silty clay loam, loamy sand and sandy loam soils and of moderate mobility in sand soils; and CAPA will be of low mobility in silty loam, loamy sand and sandy loam soils and of slight mobility in silty clay soils. Results from the 'aged soil' leaching study indicated that less than 5% of phenyl and pyridyl radioactivity was present at soil depth lower than 10 cm in both the sandy loam and loamy sand soils.

Results of terrestrial field studies of dissipation and accumulation conducted in Canada indicated that fluazinam was moderately persistent in soil, with DT_{50} values of 81.5 and 95 days with significant carryover of residues to the next season. The major transformation product, HYPA, was formed at one of the Canadian field sites reaching a maximum of 15%. HYPA was a minor transformation product at the other Canadian site. There was no evidence of leaching of fluazinam or HYPA through the soil layers. Field dissipation studies conducted in the U.S. yielded DT_{50} values of 19 and 33, indicating slight persistence. HYPA was formed as a major transformation product at one of the U.S. sites reaching 15% HYPA was a minor transformation product at the other U.S. site. Both field and laboratory studies indicate that fluazinam will be moderately persistent and have low potential to leach.

5.8 Summary of fate and behaviour in the aquatic environment

Fluazinam hydrolyzed most quickly under alkaline conditions (pH 9: half-life of 5.6 days; pH 7 half-life: 42 days) and formed one major product, CAPA. Phototransformation of fluazinam at pH 5 was rapid (half-life of 2.5 days). Abiotic phototransformation and hydrolysis in alkaline water will be important routes of transformation.

Results of two aerobic water-sediment biotransformation studies (half-lives of $\leq$ 3.2 days) and anaerobic water-sediment biotransformation studies (half-life of < 1 day) indicated that fluazinam will be non-persistent in aerobic and anaerobic aquatic systems according to the classification scheme of McEwan and Stephenson (1979). In the aerobic water-

sediment study, several major transient transformation products, DCPA, CAPA, DAPA and AMPA, were formed. In the anaerobic study, the major transformation products, DAPA, AMPA, SDS-67200, were formed.

The K_{ow} for fluazinam indicates that there is some potential for bioaccumulation. Bioconcentration factors (BCFs) of fluazinam in the bluegill sunfish were 5.8–273 µg/kg in fillet, 94–1410 µg/kg in viscera and 58–960 µg/kg in whole fish at 1 µg/L in both radiolabels. By test termination, 67, 81 and 78% of fluazinam was depurated from fillet, viscera and whole fish, respectively. Therefore, the time for 50% depuration was short (5 to 6 days).

5.9 Expected environmental concentrations

The concentrations of fluazinam in various environmental compartments were estimated based on calculations using maximum-exposure scenarios. It was assumed that, as per the label rates for Allegro 500F, a maximum of 4.0 L/ha/year at 500 g a.i. (fluazinam)/L at an interval of 7–10 days is used, equivalent to 2000 g a.i./ha/year.

5.9.1 Soil

Assuming a soil bulk density of 1.5 g/cm^3, a soil depth of 15 cm, bare soil application, and a half-life of 200 d via aerobic biotransformation in soil at 10 d spray intervals, the expected environmental concentration (EEC) of residues in soil would be 0.764 mg a.i./kg soil. The soil biotransformation study was incorporated for the EEC because it was the most conservative value and the field studies were conducted on cropped plots.

5.9.2 Aquatic systems

Direct overspray in surface water
Assuming a water density of 1 g/mL, a water depth of 30 cm and a scenario in which a body of water is over-sprayed with the product and a half-life of 3.2 d via aerobic biotransformation in water/sediment system at 10 d spray intervals, the EEC in water would be 0.075 mg a.i./L water.

Drinking water
Based on the potential use pattern of fluazinam in areas where potatoes are grown, residues of fluazinam in potential drinking water sources in these areas were calculated using the models PRZM/EXAM (for surface water) and LEACHM (for groundwater). The models were run using relevant agricultural scenarios and the environmental profile of fluazinam. There is no leaching of fluazinam to groundwater over the 20-year simulation period (0.00 µg/L). The acute surface water concentrations are 13.1 and 14.55 µg/L in reservoir and dugout, respectively, and the chronic surface water concentrations are 0.77 and 0.41 µg/L in reservoir and dugout, respectively (Table 8).

5.9.3 Vegetation and other food sources

The applicant did not submit data on the concentrations of fluazinam on crops immediately after application. Therefore, residue concentrations on vegetation were estimated using a nomogram developed by the USEPA from the data of Hoerger and Kenaga (1972) and Kenaga (1973), modified by Flether et al. (1994), using the maximum Canadian label rate for fluazinam (2000 mg a.i./kg) for use in ecological risk assessment (Urban and Cook, 1986) (Table 9). No information was available on the dissipation of fluazinam on wildlife food sources, therefore, it was assumed that no dissipation occurred. A wet weight to dry weight conversion was also calculated.

Based on the potential use pattern of fluazinam in areas where potatoes are grown, residues of fluazinam in potential drinking water sources in these areas were calculated using the models PRZM/EXAM (for surface water) and LEACHM (for groundwater). The models were run using conservative scenarios, the environmental profile of fluazinam. The values are predicting that there is no leaching of fluazinam to groundwater over the 20-year simulation period, for all 11 Level 1 scenarios (different application dates) (0.00 µg/L), and no concern for drinking water residues (acute: 13.1 and 14.5 µg/L in reservoir and dugout, respectively, chronic: 0.7 and 0.41 µg/L in reservoir and dugout, respectively).

6.0 Effects on non-target species

6.1 Effects on terrestrial organisms

The effects of fluazinam on terrestrial organisms are presented in Table 10.

Earthworms: The 28 d LC_{50} and no observed effect concentration (NOEC) values based on mortality of technical fluazinam to earthworms were >1000 and 100 mg a.i./kg artificial substrate, respectively; and the NOEC based on body weight was 10 mg a.i./kg substrate. Fluazinam is considered to be non-lethal to earthworms to and above a concentration of 100 mg a.i./kg substrate. The 14 d NOEC based on mortality and LC_{50} values of the end-use product, Allegro 500F (40% fluazinam), were 1376 and > 1376 mg a.i./kg substrate, respectively. Reduction in body weight was observed at 138 and 1376 mg product/kg substrate. Thus the NOEC based on sublethal effects was <138 mg product/kg substrate.

Honeybees: The acute 48 h oral LD_{50} and NOEC values of fluazinam to honeybees was > 100 µg/bee. The acute 48 h contact LD_{50} and NOEC values for fluazinam were >200 µg a.i./bee and 200 µg a.i./bee, respectively. In accordance with the classification of Atkins et al. (1981), fluazinam is categorized as non-toxic to bees on an acute oral and contact basis.

Birds: The acute oral 14 d LD_{50} and NOEL based on mortality of fluazinam to bobwhite quail were 1782 and 500 mg a.i./kg bw, respectively. In contrast, there were no mortalities in the mallard duck study. The acute 14 d oral LD_{50} and NOEL based on mortality to mallard ducks were > 4190 and 4190 mg a.i./kg bw, respectively. The 5 d dietary LD_{50} and NOEL based on mortality of fluazinam to bobwhite quail were >10 500 and 2480 mg a.i./kg diet, respectively; the LD_{50} and NOEL based on mortality of fluazinam to mallard ducks were >10 600 and 5230 mg a.i./kg diet, respectively. The 5 d NOEC based on body weight increase was 5230 mg a.i./kg diet in both the quail and mallard ducks. In accordance with the classification of USEPA (1985), fluazinam is categorized as moderately toxic to bobwhite quail on an acute oral basis, and practically non-toxic to bobwhite quail on a dietary basis, and practically non-toxic to mallard ducks on an acute oral and subacute dietary basis. During the one-generation reproductive study, fluazinam caused parental mortality (NOEC: 750 mg a.i./kg diet for both species), depressed body weight (NOEC: 1500 and 1000 mg a.i./kg diet for bobwhite and mallard, respectively) and reduced food consumption (NOEC: 750 and 1000 mg a.i./kg diet for bobwhite quail and mallard, respectively). Fluazinam also caused treatment-related effects on reproductive capacity in bobwhite quail including embryo viability (NOEC: 750 mg a.i./kg diet), and hatching success and 14 d old survivorship (NOEC: 500 mg a.i./kg diet); and mallard ducks including egg production, embryo viability, and 14 d old survivorship (NOEC: 500 mg a.i./kg diet) and hatching success (NOEC: 750 mg a.i./kg diet). Thus, reproductive effects were the most sensitive parameter.

Mammals: Fluazinam was considered to be of low acute oral toxicity in rats (LD_{50} > 5000 mg/kg bw) and slightly irritating to skin. In 4-week dietary studies, the NOAEL values of fluazinam for rats were 50 ppm (equivalent to 5.1 mg/kg/d and 5.3 mg/kg/d in males and females, respectively). In 90-day dietary studies, the NOAEL values of fluazinam for rats were 50 ppm (equivalent to 3.8 mg/kg/d and 4.3 mg/kg/d in males and females, respectively); NOAEL values for dog were 10 mg/kg/d. In the multigeneration reproduction study with rats (effects on pregnancy and fetuses) fluazinam did cause adverse effects. The parental NOAEL was 20 ppm (equivalent to 1.9 mg/kg/d based on liver pathology in F1 females. Reproductive NOAEL was 100 ppm (equivalent to 10.6 mg/kg/d) based on a decreased number of implantation sites and decreased litter sizes to day 4 postpartum for F1 females. Developmental toxicity NOAEL was 100 ppm (equivalent to 8.4 mg/kg/d) based on decreased body-weight gain during lactation for both F1 and F2 pups.

Terrestrial plants: Tier I study of the effect of fluazinam on germination, seedling emergence and vegetative vigour of four monocot species [corn (*Zea mays*), oats (*Avena sativa*), onion (*Allium cepa*), sorghum (*Sorghum bicolor*)] and six dicot species [cucumber (*Cucumis sativus*), radish (*Raphanus sativus*), tomato (*Lycopersicon esculentum*), soybean (*Glycine max*), and mustard (*Brassica kaber*), and buckwheat (*Fagopyrum esculentum*)] crops was performed at 0 (acetone and water control) and 1500 g a.i./ha. The EC_{25} and NOEC based on germination, emergence and fresh weight were > 1500 g a.i./ha. An additional Tier I vegetative vigour study was performed with the same species of plants at 0 and 1500 g a.i./ha. Overall, there was 29.5% inhibition of

plant weight in cucumber plants exposed to 1500 g a.i./ha. The NOEC for all other species tested was >1500 g a.i./ha. The Tier II vegetative vigour study was performed with cucumber at concentrations ranging from 0 to 1500 g a.i./ha. In contrast to the Tier I study, cucumber plants exhibited stimulatory growth in all concentrations tested. Thus, the EC_{25} is estimated at 1500 g a.i./ha based on the most conservative value from the Tier I study.

6.2 Effects on aquatic organisms

The effects of fluazinam on aquatic organisms are presented in Table 11.

Freshwater

Daphnids: The acute 48 h NOEC based on mortality and LC_{50} values of fluazinam to *Daphnia magna* in a flow-through study were 54 and 220 µg a.i./L (95% CI: 190–280 µg a.i./L), respectively, in a flow-through test. The 48 h NOEC based on mortality and LC_{50} values to the same species in a static test were < 55.5 and 220 µg a.i./L (95% CI: 197–246 µg a.i./L), respectively. Based on the results of these studies, fluazinam would be classified as highly toxic to daphnids in accordance with the classification system of the USEPA. The 21 d chronic NOEC and LC_{50} based on parental daphnid mortality were 68 and >140 µg a.i./L, respectively. The NOEC based on reproduction (number of young produced per female) of fluazinam to daphnids was 140 µg a.i./L.

Fish: The chronic 96 h LC_{50} values of fluazinam to juvenile rainbow trout (*Oncorhynchus mykiss*) in two separate studies were 111 µg a.i./L (95% CI: 100–130 µg a.i./L) and 36 µg a.i./L (95% CI: 33–56 µg a.i./L), respectively. The chamber conditions were the same for both studies except for hardness which was 50–56 and 28–30 mg/L $CaCO_3$ in the first and second study, respectively. The corresponding NOEC values based on mortality in the two studies were 64 and 28 µg a.i./L, respectively. The chronic 96 h LC_{50} value of fluazinam to juvenile bluegill sunfish (*Pimephales promelas*) under flow-through conditions was 55 µg a.i./L. The corresponding NOEC value based on mortality was 21 µg a.i./L. Based on the results of these studies, fluazinam would be classified as highly toxic to very highly toxic to rainbow trout and very highly toxic to bluegill sunfish in accordance with the classification system of the USEPA (1985). The 34 d chronic early life stage NOEC for fathead minnow based on mortality and hatching success were 5.3 and 10 µg a.i./L, respectively. The 278 d chronic full life cycle $NOEC_{F0\ generation}$ values based on survival and reproductive success were 6.4 and 2.9 µg a.i./L, respectively. The $NOEC_{F1\ generation}$ values based on hatching success was 0.69 µg a.i./L. Based on the results of this study, the most sensitive endpoint was F_1 generation hatching success.

Algae: The chronic 96 h EC_{50} of fluazinam to green algae, *Selenastrum capricornutum*, based on cell density, biomass (area under the curve) (E_bC_{50}), and growth rate (E_rC_{50}) were 0.18, 0.15 and >0.20 mg a.i./L, respectively. The corresponding NOEC values were 0.048, 0.048 and 0.082 mg a.i./L, respectively. The most sensitive endpoint was biomass (NOEC: 0.048 mg a.i./L).

The 7 d EC_{50} of fluazinam to duckweed, *Lemna gibba*, based on frond number and biomass (E_bC_{50}) were both > 53.6 µg a.i./L. The NOEC based on frond number and biomass were both 28.8 µg a.i./L.

Marine

Shrimp: The 96 h NOEC based on mortality and LC_{50} values of fluazinam to mysid shrimp (*Mysidopsis bahia*) were 13 and 39 µg a.i./L, respectively. Based on the results of this study, fluazinam is categorized as very highly toxic to mysid shrimp in accordance with the classification system of the USEPA (1985).

Oyster: The 96 h NOEC and EC_{50} values based on shell deposition of fluazinam (96.8% purity) to the Eastern oyster (*Crassostrea virginica*) were 1.4 and 4.0 µg/L, respectively. Based on the results of this study, fluazinam would be classified as very highly toxic to the eastern oyster in accordance with the classification system of the USEPA (1985).

Fish: The 96 h NOEC based on mortality and LC_{50} values of fluazinam to juvenile sheepshead minnow (*Cyprinodon variegatus*) were 80 and 120 µg a.i./L (95% CI: 80 to 240 µg a.i./L), respectively. Based on the results of this study, fluazinam is classified as highly toxic to sheepshead minnow (*Cyprinodon variegatus*) in accordance with the classification system of the USEPA (1985).

6.3 Effects on biological methods of sewage treatment

Data are not currently required by the PMRA.

6.4 Risk characterization

6.4.1 Environmental behaviour

Fluazinam is relatively stable to hydrolysis at pH 5 and pH 7, but rapidly hydrolyses at pH 9 and rapidly phototransforms in aquatic systems. Fluazinam is non-persistent to slightly persistent in aerobic and anaerobic aquatic systems. Fluazinam is non-persistent under anaerobic soil conditions, and is slightly persistent to persistent under aerobic soil conditions. Under field conditions, fluazinam was slightly persistent to moderately persistent, depending on site location and temperature, with up to 52% carryover of residues to the next season. Fluazinam has a very low potential to leach through the soil. The principal routes of transformation are biotransformation in the soil and aquatic environment, phototransformation in the aquatic environment and hydrolysis. Fluazinam is readily taken up by fish, but is depurated unmetabolized within 6 days of uptake. Fluazinam has low potential to volatilize from water and moist soils. Under most laboratory soil and water/sediment conditions, the major transformation products, HYPA, CAPA, MAPA and AMPA, declined by test termination, indicating low to moderate persistence. The major hydrolysis transformation product, CAPA, was still increasing at test termination. Under terrestrial field conditions, only HYPA was formed in excess of 10% and declined to <1% after 365 days.

6.4.2 Terrestrial organisms

Earthworms: Based on the NOEC (mortality) and LC_{50} for earthworms (100 and >1000 mg a.i./kg dw substrate, respectively) and the maximum EEC of fluazinam in soil (0.764 mg a.i./kg soil), fluazinam poses a negligible risk for death to earthworms at the proposed maximum application rate. The risk quotient (EEC/NOEC) is 0.0076. Based on weight loss (NOEC: 10 mg a.i./kg substrate), fluazinam poses a negligible risk for weight loss to earthworms at the proposed maximum application rate. The risk quotient (EEC/NOEC) is 0.0764. As the maximum EEC for Allegro 500F in soil is 1.91 mg a.i./kg soil (0.764 mg a.i./kg soil ÷ 0.40 (% a.i.)), and the NOEC (mortality) and LC_{50} values were 1376 and >1376 mg product/kg dw substrate, respectively, Allegro 500F also poses negligible risk for death to earthworms at the proposed maximum application rate. The risk quotient (EEC/NOEC) is 0.0014.

Honeybees: The chronic contact and oral 48 h LD_{50} values of fluazinam were > 200 and > 100, respectively. The corresponding NOEC values were 200 and 100 μg a.i./bee. According to Atkins et al (1981), fluazinam poses a negligible hazard to honeybees.

Wild birds: Wild birds, such as mallard duck and bobwhite quail, could be exposed to fluazinam residues as a result of spray drift or consumption of sprayed vegetation or contaminated prey. The mallard duck diet may consist of approximately 30% arthropods and 70% grain (USEPA 1993). The bobwhite quail diet may consist of approximately 30% small insects, 15% forage crops, and 55% grain and seeds. Since the EECs of fluazinam for mallard ducks on arthropods and grain are 67.64 and 67.40 mg a.i./kg dw, respectively (Table 12), the estimated ingestion of fluazinam through contaminated food sources by the mallard can be calculated as follows:
$(0.3 \times 67.64) + (0.70 \times 67.40) = 67.47$ mg a.i./kg dw

Since the EECs of fluazinam for bobwhite quail on small insects, forage crops, and grains and seeds are 395.19, 1296.01 and 67.64 mg a.i./kg dw, respectively (Table 12), the estimated ingestion of fluazinam through contaminated food sources by the bobwhite quail can be calculated as follows:
$(0.3 \times 395.19) + (0.15 \times 1296.0) + (0.55 \times 67.40) = 350.03$ mg a.i./kg dw

Chronic oral toxicity studies: In the chronic oral toxicity study of fluazinam on bobwhite quail, the mean body weight of an individual (BWI) of the quail in the control treatment was 0.193 kg bw/individual, while the mean food consumption (FC) was 0.019 kg dw of diet/individual/d. The potential daily intake of fluazinam (DI = FC × EEC) was calculated as 6.65 mg a.i./individual/d. The reported LD_{50} and NOEL values were 1782 and 500 mg a.i./kg bw, respectively. When expressed on a per individual basis, the LD_{50} (individual) (= LD_{50} × BWI) was 343.9 mg a.i./individual, and the NOEL based on mortality (individual) (= NOEC × BWI) was 96.5 kg bw/individual. Based on the daily intake (DI), the LD_{50} (individual) and the NOEC (individual), it would take a bobwhite quail at least 14.5 d (96.5 kg bw/individual ÷ 6.65 mg a.i./individual/d) of consumption of a contaminated diet to attain the dose equivalent to that administered in the laboratory by

gavage that had no observable effect on the laboratory population. Since it takes longer than one day to reach the NOEC for mortality, fluazinam poses a negligible risk to bobwhite quail.

In the chronic toxicity study of fluazinam on mallard ducks, the mean BWI of mallard in the control treatment was 1.06 kg bw/individual, while the mean food consumption (FC) was 0.071 kg dw of diet/individual/d. The potential daily intake of fluazinam (DI = FC × EEC) was calculated as 4.79 mg a.i./individual/d. The reported LD_{50} and NOEL values were > 4190 and 4190 mg a.i./kg bw, respectively. When expressed on a per individual basis, the LD_{50} and NOEC based on mortality and body weight (individual) (= LD_{50} × BWI) were both 4441.4 mg a.i./individual. Based on the DI, the LD_{50} (individual) and the NOEC (individual), it would take a mallard duck at least 925 days of consumption of a contaminated diet to attain the dose equivalent to that administered in the laboratory by gavage that had no observable effect on the laboratory population. Since it takes longer than one day to reach the NOEC for mortality, fluazinam poses a negligible risk to mallard ducks.

Short-term dietary studies: The 8 d LC_{50} values in bobwhite quail and mallard duck were >10 500 and >10 600 mg a.i./kg diet, respectively. The corresponding NOEC values based on mortality were 2480 and 5230 mg a.i./kg diet, respectively. Based on the EECs, fluazinam will pose a low dietary risk to bobwhite quail (risk quotient (RQ) (EEC/NOEC) = 0.13) and a negligible risk to mallard ducks (RQ (EEC/NOEC) = 0.01).

Reproductive dietary studies: The 22-week NOEC based on reproductive success was 500 mg a.i./kg diet, in both bobwhite quail and mallard ducks. In the bobwhite quail study, hatching success and 14 d old chick survivorship was significantly reduced. In the mallard duck study, egg production, embryo viability and 14 d old chick survivorship was significantly reduced. Based on the EECs, fluazinam will pose a low reproductive risk to the bobwhite quail (RQ (EEC/NOEC) = 0.700) and mallard ducks (RQ (EEC/NOEC)=0.14).

Wild mammals: Wild mammals, such as rats and mice, could be exposed to residues of fluazinam as a result of the consumption of sprayed vegetation and/or contaminated prey. From Table 12, assuming no transformation, the EECs of fluazinam in the diets of rats and mice were 1008.99 and 1002.93 mg a.i./kg dw diet, respectively.

In the assessment of the chronic risk to rats, default values were used for food consumption (FC: 0.06 kg dw/ind/day) and body weight per individual (BWI: 0.350 kg bw/ind). The EEC was 1008.99 mg a.i./kg dw for rats. The DI (DI = FC × EEC) was calculated as 60.54 mg a.i./ind/day for rats. No data were available for mice.

The LD_{50} in this study was >5000 mg a.i./kg bw for fluazinam. Expressed on a per individual basis, the LD_{50} (ind) (LD_{50} × BWI) is 1750 mg a.i./ind. Thus, the number of days of intake by a wild rat to accumulate a dose equivalent to that administered by gavage that killed 50% of a laboratory population would be 28.9 days.

As NOAEL values were not available for chronic oral toxicity, one-tenth of the LD_{50} value (500 mg a.i./kg bw) was used as the NOAEL. Thus, the maximum number of days of intake by a wild rat to attain a dose equivalent to that administered by gavage to a laboratory population of rats that had no observable effect is also one-tenth of the number of days required to accumulate a dose equivalent to that administered by gavage that killed 50% of the laboratory population. From the studies with fluazinam, the maximum number of days of intake to reach the laboratory dosage that had no observable effect is 2.9 days.

Based on the above assessments, applications of fluazinam at the proposed label rates pose a negligible chronic risk to populations of wild mammals that are exposed through consumption of sprayed dietary items.

Dietary studies were conducted with fluazinam on rats. The NOAEL values for the 4-week study was 50 mg/kg dw (equivalent to 5.1 mg/kg/d in males and 5.3 mg/kg/d in females). Using an EEC of 1008.99 mg a.i./kg dw for rats, there would be a high dietary risk to rats (RQ (EEC/NOEC) = 20). The NOAEL values for the 90-day study were 50 mg/kg dw (equivalent to 3.8 mg/kg/d in males and 4.3 mg/kg/d in females). Using an EEC of 1008.99 mg a.i./kg, there would be a high dietary risk to rats (RQ (EEC/NOEC) = 20).

In a reproductive study conducted with rats, the most sensitive reproductive NOAEL value was 100 mg/kg dw (equivalent to 10.6 mg/kg/d) for parental rats. Using an EEC of 1008.99 mg a.i./kg dw, there would be a high reproductive risk to rats (RQ (EEC/NOEC) = 10.1).

Terrestrial plants: The results of a Tier I phytotoxicity study conducted with fluazinam indicated that the estimated EC_{25} for the most sensitive endpoint for vegetative vigour, plant weight, in cucumber, was 1500 g a.i./ha. The EEC is the maximum application rate (2000 g a.i./ha). These results indicate that fluazinam will pose a moderate risk to vegetative vigour of cucumber plants if exposure of non-target vegetation occurs by overspray. The risk quotient (EEC/EC_{25}) is 1.3. It was noted, however, that the EC_{25} in two other Tier I tests were >1500 g a.i./ha in cucumber plants, and growth was actually stimulated in several monocot and dicot species.

6.4.3 Aquatic organisms

Freshwater

Invertebrates: The most sensitive acute and chronic NOEC values for *Daphnia magna* were 54 µg a.i./L (mortality) and 68 µg a.i./L (parental mortality), respectively. Since the EEC in water was 75 µg a.i./L, fluazinam poses a moderate risk to daphnids based on chronic exposure (RQ (EEC/NOEC) = 1.1) and an acute basis (RQ (EEC/NOEC) = 1.39).

Fish: The most sensitive acute endpoint was the NOEC based on mortality for bluegill sunfish, which was 21 µg a.i./L, and the most sensitive chronic endpoint was the NOEC based on reproduction (hatching success of F_1 generation fish) for fathead minnow, which was 0.69 µg a.i./L. Fluazinam poses a moderate risk of mortality to bluegill sunfish (RQ (EEC/NOEC) = 3.57) based on acute exposure, and a very high reproductive risk to fathead minnow based on chronic exposure (RQ (EEC/NOEC) = 108.7). Since Allegro 500F is applied 10 times per season, it is possible that fish will be continuously exposed to fluazinam during the breeding season. Thus, the chronic NOEC will be used in the risk assessment.

Algae: The most sensitive acute endpoint was the NOEC based on biomass for green algae, which was 48 µg a.i./L. Based on the EEC, fluazinam poses a moderate risk for reduction of biomass in algae based on acute exposure (RQ (EEC/NOEC) = 1.56).

Vascular plants: The most sensitive acute endpoint was the NOEC based on biomass or frond number for duckweed, which were both 28.8 µg a.i./L. Based on the EEC, fluazinam poses a moderate risk for reduction of frond number and biomass in duckweed based on acute exposure (RQ (EEC/NOEC) = 2.6).

Marine

Invertebrates: The most sensitive acute NOEC based on shell growth for Eastern oyster was 1.4 µg a.i./L. Since the EEC in water was 75 µg a.i./L, fluazinam poses a high risk of reduced shell growth to Eastern oyster based on acute exposure (RQ (EEC/NOEC) = 53.6).

Fish: The most sensitive acute NOEC based on mortality for sheepshead minnow was 80 µg a.i./L. Since the EEC in water was 75 µg a.i./L, fluazinam poses a low risk of mortality to sheepshead minnow based on acute exposure (RQ (EEC/NOEC) = 0.94).

6.5 Risk mitigation

Fluazinam is of very high toxic risk to freshwater aquatic organisms, of high toxic risk to marine aquatic organisms, and of high dietary and reproductive risk to wild mammals.

During the environmental review of fluazinam and its end-use products, Allegro 500F (40% fluazinam), the PMRA determined that buffer zones were required to mitigate the risk to freshwater and marine aquatic organisms.

The following labelling is required.

On the container label, under "ENVIRONMENTAL HAZARDS:", insert the following:

"Observe buffer zones specified under Directions for Use."
"This product is toxic to fish."
"This product is toxic to wild mammals."

Based on the persistence of fluazinam and high potential for carryover, which may detrimentally affect organisms, the following statement must be added to the ENVIRONMENTAL HAZARDS section of the label for the end-use product:

> "Fluazinam is persistent and will carryover; it is recommended that the product, Allegro 500F Crop Fungicide containing fluazinam, not be used in areas treated with this product during the previous season."

On the container label, under "DIRECTIONS FOR USE":, insert the following:

> "Do not apply during periods of dead calm or when winds are gusty. Do not overspray non-target terrestrial or aquatic habitats. Do not contaminate aquatic habitats when cleaning and rinsing spray equipment or containers."

> "A buffer zone of 26 metres is required between the downwind point of direct application and the closest edge of sensitive aquatic habitats such as lakes, rivers, sloughs, ponds, coulees, prairie potholes, creeks, marshes, streams, reservoirs, and wetlands. A buffer zone of 19 metres is required between downwind point of direct application and the closest edge of estuarine/marine habitats."

7.0 Efficacy

7.1 Effectiveness against target organisms, or with respect to the effect achieved

7.1.1 Intended use

Allegro 500F Fungicide, containing 500 g/L fluazinam, is proposed for control of late blight on potatoes. The proposed application rate is 0.4 L product/ha. By active ingredient, the proposed rate is:

Active Ingredient	Application Rate	
	mL/ha	gram a.i./ha
fluazinam	400	200

7.1.2 Mode of action

Fluazinam is a non-systemic protectant fungicide, belonging to the chemical group, 2,6-dinitroanilines. Fluazinam is an uncoupler of oxidative phosphorylation in the respiration chain involving protonation/deprotonation.

7.1.3 Nature of the pest problem

Late blight is one of the most devastating diseases in potato production worldwide. The causal agent, *Phytophthora infestans*, survives mainly in abandoned potato plant material in fields, cull piles and gardens. All parts of potatoes are susceptible. Symptoms first appear as pale green water-soaked spots, often beginning at the leaf tips or edges. The circular or irregularly shaped lesions are often surrounded by a pale yellowish green border that merges with the healthy tissue. Lesions enlarge rapidly and turn brown or purplish black. During periods of high humidity, lesions may be bordered with a white mold growth on the underside of the leaf. In dry weather, infected leaf tissue turns brown and quickly dries up. Infected stems and petioles turn brown to black and entire vines may become blackened. In addition to blighting foliage, the fungus can infect potato tubers. Affected tubers first show brownish blotch on the outer edge before harvest. The disease continues to develop after the crop is harvested, causing the potatoes to rot in storage. Late blight may result in total plant loss or death from early infection and severe reduction of the yield.

7.1.4 Effectiveness against pest

Results were submitted from 19 field trials conducted in Canada and northern U.S. between 1992 and 1999 which assessed the performance of Allegro 500F. Allegro was compared with a commercial standard and an untreated check. Crops were evaluated for disease severity by rating percent foliage infection and yield.

1. Application rate:

In ten studies, fluazinam was applied at 193–234 g a.i./ha, close to the proposed rate of 200 g a.i./ha. All the studies showed significant difference between fluazinam and the untreated check. The data also indicated that fluazinam provided the same level of disease severity/incidence control as the commercial standards, i.e., fluazinam provided an average of 82% disease severity control and 88% disease incidence control while chlorothalonil provided an average of 76% disease severity control and 86% disease incidence control, and mancozeb provided an average of 86% disease severity control.

Two studies applied fluazinam at lower than the proposed rates (18.75, 37.5, 75, 150 g a.i./ha); statistical analysis was not submitted for these studies. However, the data showed that the higher the rate, the higher the control level. The proposed rate of 200 g a.i./ha was not included as a treatment. Indirect comparison showed that fluazinam, when applied at 0.75 of the proposed rate (150 g a.i./ha), provided an average of 72% disease severity control, compared with fluanizam at 200 g a.i./ha in other trials, which provided an average of 82% disease severity control.

A review of the data supports the proposed application rate at 200 g a.i./ha.

2. Spray volume:

All the studies were conducted with the diluted spray. The spray volume ranged from 200 to 600 litres per hectare. No data were generated at the low ground spray volumes of 50–100 litres per hectare. Therefore, the low ground spray volume of 50–100 litres per hectare is not supported.

A review of the data supports the diluted spray volume between 200 and 600 litres per hectare.

3. Application interval:

Five studies were conducted under high disease pressure. The data showed that the 7-day interval provided adequate disease severity/incidence control. Two studies were conducted under low to moderate disease pressure. The data showed that the 10-day interval provided adequate disease severity/incidence control.

A review of the data supports the proposed claim of fluazinam with a 7-day application interval under high disease pressure and a 10-day application interval under low disease pressure.

4. Number of applications:

The number of applications in the field studies ranged from four to nine. The available data showed that nine applications at 584 g a.i./ha (2.6 times higher than the proposed maximum amount per season) did not cause adverse effects. Late blight may affect potatoes at all growth stages. A season-long preventative late blight control program might require, when conditions are favourable to disease development, up to 18 preventative fungicide applications during the growing season. Therefore, given the need for season-long control for this disease, the proposed maximum of 10 applications of fluazinam per growing season is acceptable.

7.2 Phytotoxicity to target plants or target plant products

No independent crop tolerance studies were conducted. However, most studies had observations about phytototoxicity and yield data which showed no adverse effects. The information available indicates that it is safe to use Allegro 500F at the proposed rate of 200 g a.i./ha on potatoes.

7.3 Impact on succeeding crops, adjacent crops and on treated plants or plant products used for propagation

No information was provided.

7.4 Economics

No information was provided.

7.5 Sustainability

7.5.1 Survey of alternatives

7.5.1.1 Non-chemical control practices

Reducing the amount of initial inoculum is a critical management strategy to control late blight. Cultural control methods include eliminating all potato cull piles in the vicinity of potato, tomato and pepper field and destroying volunteer potato plants that grow from overwintered tubers. Planting infected seed tubers should be avoided. Reducing periods of leaf wetness (e.g., irrigation) can reduce secondary infection. Practices that optimize growing conditions through proper fertilizer, water and pest management will reduce plant stress and, therefore, decrease the severity of late blight and early blight.

7.5.1.2 Chemical control practices

The major alternative fungicide active ingredients currently registered for control of the pests on the proposed crops include, but are not necessarily limited to, the following:

Pest	Crop	Available alternative active ingredient	Fungicide group
Late blight	Potatoes	Inorganics (copper hydroxide, copper oxychloride, copper sulphate)	M
		Triazines (anilazine)	M
		Phthalimides (captan)	M
		Dithio-carbamate (zineb, mancozeb, maneb, metiram)	M
		Chloronitriles (chlorothalonil)	M
		Cinnamic acids (dimethomorph)	15
		Acylalanines (metalaxyl-m)	4
		Carbamates (propamocarb)	28
		Cyanoacetamide oxime (cymoxanil)	27
		Benzamides (zoxamide)	22
		Methoxy-carbamates (pyraclostrobin)	11
		Oxazolidinediones (famoxadone)	11

7.5.2 Compatibility with current management practices including integrated pest management

A number of disease management practices, in addition to chemical control, are available to growers of the target crops. For control of late blight on potatoes, it is essential to employ early management strategies to minimize the introduction of inoculum into the field and to monitor blight development using disease prediction models relevant to the production area. As a foliar fungicide, Allegro 500F is compatible with these practices.

7.5.3 Contribution to risk reduction

Allegro 500F fits well into IPM strategies due to its strong activity on late blight disease. It is a potential alternative to some of the older fungicides currently used for control of late blight on potatoes.

7.5.4 Information on the occurrence or possible occurrence of the development of resistance

Fluazinam belongs to the group 29 fungicide and is classified by the Fungicide Resistance Action Committee (FRAC) as a low resistance risk product. This classification is supported by the fact that fluazinam has been used in Europe for 10 years for control of late blight at 200 g a.i./ha, applied season-long (between 10 and 14 applications per year) without the development of resistance.

The following resistance management statements have been added to the label according to Regulatory Directive DIR99-06 entitled *Voluntary Pesticide Resistance-Management Labelling Based on Target Site/Mode of Action*.

GROUP	29	FUNGICIDE

Resistance management recommendations

Allegro 500F Agricultural Fungicide contains fluazinam, a group 29 fungicide. Any fungal population may contain individuals naturally resistant to Allegro 500F Agricultural Fungicide and other group 29 fungicides. The resistance biotypes may dominate the fungal population if these fungicides are used repeatedly in the same field. Other resistance mechanisms that are not linked to the site of action, but specific for individual chemicals, such as enhanced metabolism, may also exist. Appropriate resistance-management strategies should be followed.

To delay fungicide resistance:

- Do not make more than three consecutive applications of Allegro 500F before alternating with fungicides having a different mode of action other than group 29 fungicide.
- Apply a maximum of 10 applications per year.
- Fungicide use should be based on an integrated pest management (IPM) program that includes scouting and record keeping and considers cultural, biological, and other chemical control practices.
- Monitor efficacy of all fungicides used in the disease management program against the target pathogen and record other factors that may influence fungicide performance and/or disease development.
- Contact the local extension specialist or certified crop advisors for any additional pesticide resistance-management and IPM recommendations for specific site and pest problems in the area.
- For further information or to report suspected resistance, contact Dr. Myron Bliss Jr. at 1-440-357-4561 (Long distance charges apply) or at blissm@iskbc.com.

7.6 Conclusions

The claim for control of late blight (*Phytophthora infestans*) on potatoes is supported.

Table 1 Value summary

Proposed		Recommendation (based on value assessment)	Comments
Crop/Pest	**Details**		
Potatoes			
Late blight	Apply at 400 mL per hectare on a 7- to 10-day schedule. Maximum 4 L product per hectare per growing season.	10 applications at 400 mL per hectare on a 7- to 10-day schedule.	Do not make more than three consecutive applications of Allegro 500F before alternating to a fungicide with a different mode of action.

8.0 Toxic Substances Management Policy considerations

During the review of fluazinam and the end-use product Allegro 500F fungicide, the PMRA has taken into account the federal Toxic Substances Management Policy[1] and has followed its Regulatory Directive DIR99-03[2]. It has been determined that this product does not meet TSMP Track-1 criteria because:

- Fluazinam does not meet the criteria for persistence in water and sediment. Its values for half-life in water, and sediment in whole water/sediment system are below the TSMP Track-1 cut-off criteria for water (> 182 d), soil (>182 d), and sediment (>365 d). However, fluazinam does meet the cut off criteria for soil based on laboratory studies. Fluazinam is not expected to volatilize from water or moist soil surfaces.

- Fluazinam is not bioaccumulative. Studies have shown that the BCF is 1850, which is below the TSMP Track-1 cut-off criterion of BCF ≥5000. The log K_{ow} is 4.03 which is also below the TSMP Track-1 cut-off criteria (log K_{ow} >5). Based on bioaccumulation studies, fluazinam is depurated within 6 days and is excreted in its parent form.

- The toxicity of fluazinam is described (see Sections 3.6, 4.7 and 6.4).

- The hydrolysis transformation product, CAPA, reached maximum concentrations at test termination (day 28), thus the persistence of CAPA is unknown.

- Fluazinam (technical grade) does not contain any by-products or microcontaminants that are TSMP Track-1 substances as identified in App. II of DIR99-03. Impurities of toxicological concern as identified in Section 2.13.4 of DIR98-04 and TSMP Track-1 substances are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process. It should be noted that "Impurity no. 5" is carried over from the TGAI to the EP as it is not formed from the formulation process.

The formulated product does not contain any formulants that are known to contain TSMP Track-1 substances.

9.0 Regulatory decision

Fluazinam and the end-use product Allegro 500F have been granted temporary registration for use for the control of late blight on potatoes, pursuant to Section 17 of the Pest Control Products Regulations, subject to the following conditions:

- Subchronic neurotoxicity study in rats
- Developmental neurotoxicity study in rats
- 7-day inhalation study in rats
- Mechanistic study
- Octanol–water partition coefficient for CAPA
- Reduce level of impurity no. 5 to 0.1%
- Hydrolysis study with CAPA
- Toxicity of SDS-67200 to benthic dwelling species.

List of abbreviations

1D-TLC	1-Dimensional Thin layer chromatography
2D-TLC	2-Dimensional Thin layer chromatography
ACN	acetonitrile
ADI	acceptable daily intake
a.i.	active ingredient
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMGT	3-[[4-amino-3-[[3-chloro-5-(trifluoromethyl)-2-pyridinyl] amino]-2-nitro-6-(trifluoromethyl)phenyl]thio]-2-(β-D-glucopyranosyloxy) propionic acid
AMPA	4-Chloro-N^2-[3-chloro-5-(trifluoromethyl)-2-pyridyl]-3-nitro-5-(trifluoromethyl)-1,2-benzenediamine
ARfD	acute reference dose
AST	aspartate amino-transferase
B-1457	N-[3-chloro-2,4-dinitro-6-(trifluoromethyl)phenyl-5-(trifluoromethyl)-2-pyridinamine, CAS number 169327-87-1
bw	body weight
bwg	body-weight gain
CAPA	5-chloro-6-(3-chloro-α,α,α-trifluoro-2,6-dinitro-p-toluidino)nicotinic acid
CAS Number	Chemical Abstracts Service Registry Number
CEC	cation exchange capacity
cm	centimeters
d	day(s)
DACO	data code
DAPA	3-chloro-2-(2,6-diamino-3-chloro-α,α,α-trifluoro-p-toluidino)-5-(trifluoromethyl) pyridine
DAT	days after treatment
DCPA	6-(4-carboxy-3-chloro-2,6-dinitroanilino)-5-chloronicotinic acid
DNA	deoxyribonucleic acid
DNT	developmental neurotoxicity
DT_{50}	dissipation time 50%
dw	dry weight
EC_{50}	effective concentration 50%
ECD	Electron Capture Detector
EEC	expected environmental concentration
EU	European Union
F_0	parental animals
F_1	1st generation offspring
F_2	2nd generation offspring
FDA	Food and Drug Administration
FLC	flowable concentrate
FOB	functional observational battery
FQPA	*Food Quality Protection Act*
fw	fresh weight
g	gram

GC	gas chromatography
GD	gestation day
GLC	gas-liquid chromatography
GLP	good laboratory practices
h	hour
ha	hectare
HCl	hydrochloric acid
HPLC	high-performance liquid chromatography
HYPA	5-[(3-chloro-5-(trifluoromethyl)-2-pyridyl)amino]-α,α,α-trifluoro-4,6-dinitro-o-cresol
K_{ow}	octanol–water partition coefficient
K_d	adsorption quotient
K_{oc}	adsorption quotient normalized to organic carbon
kg	kilogram
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOEC	lowest observed effect concentration
LOD	level of detection
LOQ	level of quantification
LSC	liquid scintillation counter
MAPA	3-Chloro-N^1-[3-chloro-5-(trifluoromethyl)-2-pyridinyl]-6-nitro-4-(trifluoromethyl)-1,2-benzenediamine
m	metre
MAS	maximum average score
mg	milligram
MIS	maximum irritation score
mL	millilitre
MMAD	mass median aerodynamic diameter
mm Hg	millimetre of mercury
MOS	margin of safety
MRL	maximum residue limit
MS	mass spectrometry
mV	redox potential
NAC	N-acetyl cysteine
ng	nanogram
nm	nanometre
NMR	Nuclear magnetic resonance
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NPD	Nitrogen-phosphorus detection
OC	organic carbon
OECD	Organisation for Economic Co-operation and Development
OM	organic matter
PES	post-extraction solids

PHI	pre-harvest interval
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppb	parts per billion
ppm	parts per million
RAC	raw agricultural commodity
RBC	red blood cell
ROC	residue of concern
RPLC	reverse-phase liquid chromatography
RQ	risk quotient
SDS-67230	2-chloro-6-[(3-chloro-5-(trifluoromethyl)-2-pyridyl)-α,α,α-trifluoro-5-nitro-*m*-cresol
SGPT	alanine amino-transferase
TFA	trifluoroacetic acid
TGAI	technical grade active ingredient
TLC	thin layer chromatography
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
UF	uncertainty factor
µg	microgram
µL	microlitre
UK	United Kingdom
USEPA	United States Environmental Protection Agency
UV	ultraviolet
vol	volume
v:v	volume per volume
w:v	weight per volume
WBC	white blood cell

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Appendix I Summary Tables

Table 1 Methods for analysis of the active substance as manufactured

Product	Analyte	Method Type	Linearity range	Recovery (%) (n)	RSD (%) (n)	LOQ (%)	Method
Technical	Fluazinam	RPLC/UV at 240 nm	1.03–2.95 mg/mL	99.5–100.2 (3)	0.17–0.82 (5)	N/R	Accepted
Technical	Major impurities	RPLC/UV at 240 nm	0.03–11%	77.3–194.1 (3 each)	0.17–2.57 (5 each)	0.005–0.02	Accepted

Table 2 Methods for formulation analysis

Product	Analyte	Method Type	Linearity range (mg/100 mL)	Mean % Recovery (n)	RSD (%) (n)	Method
Allegro 500F	Fluazinam	RPLC/UV at 236 nm	0.17–0.24 mg/mL	99.8 ± 0.11% (3)	0.13% (8)	Accepted

Table 3 Methods for environmental residue analysis

Summary of method validation data for residues of fluazinam and transformation products in soil, sediment and water and biota								
Matrix	**Analytical parameter**	**% Recovery (n)**						**Method (N/A) ***
		Fluazinam	**DAPA**	**MAPA**	**HYPA**	**CAPA**	**AMPA**	
Soil	Method	GC/ECD	HPLC/UV	GC/ECD	GC/ECD	GC/ECD	HPLC/UV	Accepted
	Spike level (ppm)	0.01–0.30	0.02 – 3.0	0.01 – 0.30	0.01 – 0.25	0.01–0.25	0.02–3.0	
	Mean % recovery (n)	101 ± 13 (57)	82.5 ± 1.8 (20)	104 ± 15 (49)	98 ± 1.9 (41)	93 ± 18 (42)	80.8 ± 2.7 (20)	
	LOQ	0.01 ppm		0.01 ppm	0.01 ppm	0.01 ppm		
	LOD		0.02 ppm				0.02 ppm	
Sediment	The HPLC Method for AMPA and DAPA (major transformation products in sediment) in soil was extended to sediment as the overall recoveries of AMPA spiked at 0.02 – 2.0 ppm in soil and in sediment were 73.4 ± 10.6% and 63.0 ± 10.5%, respectively.							Accepted
Water, runoff and surface	Method	GC/ECD	ISK has submitted a waiver for the analytical method for hydrolysis products (AMPA and DAPA) which was accepted by EAD.					Accepted
	Spike level (ppm)	0.01 – 0.5						
	Mean % recovery (n)	92.7±19.5 (7)						
	LOQ	0.1 ppb						

Summary of method validation data for residues of fluazinam and transformation products in soil, sediment and water and biota								
Matrix	**Analytical parameter**	**% Recovery (n)**						**Method (N/A) ***
		Fluazinam	**DAPA**	**MAPA**	**HYPA**	**CAPA**	**AMPA**	
Peanut	Method	GC/ECD	No method for metabolites submitted.					Accepted
	Spike level (ppm)	0.01 – 20.0						
	Mean % recovery (n)	91 ± 11.5 (4)						
	LOQ	0.01 ppm						
Cow liver and muscle (loin and chuck)	Method	GC/ECD	No method for metabolites submitted.					Accepted
	Spike level (ppm)	0.01 – 1.0						
	Mean % recovery (n)	99.9 ± 15.4 (19)						
	LOQ	0.01 ppm						

Table 4 Toxicology

METABOLISM

A series of studies was conducted to assess the absorption, excretion, distribution, and metabolism of IKF-1216 (Fluazinam) in rats following oral administration.

A pilot study using 3 male and 3 female rats given single gavage doses of Fluazinam (0.5 or 50 mg/kg) was conducted to assess excretion patterns at 48 hours. Subsequent experiments using groups of 5 male and 5 female rats given single or 14-day repeated doses of test material (0.5 or 50 mg/kg) generated more comprehensive data for assessing excretion pathways, plasma elimination kinetics, tissue distribution and metabolism of the test article.

Absorption
Approximately 33–40% of the test material was absorbed from the gastrointestinal tract. Most appears to undergo simple enterohepatic uptake followed by biliary excretion. The majority of fluazinam that is absorbed into the systemic circulation is eliminated within 48 hours.
Distribution
Tissue burdens of fluazinam-derived radioactivity were minimal with tissues and organs associated with the gastrointestinal tract exhibiting the highest concentrations. Fluazinam does not appear to have a potential to accumulate in the body.
Excretion
Fecal elimination as both unabsorbed parent compound and biliary excretory products were the major route of excretion and generally accounts for 90% of the administered dose. Excretion via expired air is negligible (<0.1%) and urinary excretion is a minor route (1–4%). Within 48 hours, 85–95% of administered fluazinam was excreted.
Metabolism
Orally administered fluazinam does not appear to be sex-dependent in rats and may exhibit saturation kinetics at the high dose. However, the apparent decrease in metabolite formation may be more a function of saturation of gastrointestinal absorption than saturated metabolic pathway(s). The most frequently seen metabolites are AMPA, DAPA and some related conjugates and hydrolysis products.

Fluazinam Technical

STUDY and MRID	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/SIGNIFICANT EFFECTS/ COMMENTS
ACUTE STUDIES			
Oral	95.3%, SD rats, 2.5, 3.2, 4.0 and 5 g/kg bw, 5/sex/dose	LD_{50} = 4.3 g/kg bw combined ♂ 4.5 g/kg bw ♀ 4.1 g/kg bw Low Toxicity	5.0 g/kg – 4/5 ♂, 4/5 ♀ died 4.0 g/kg – 1/5 ♂, 3/5 ♀ died Signs of abnormal body carriage, abnormal gait, lethargy, ataxia, pallor of extremities, piloerection, and diarrhea
Oral	97.9%, CD rats, 5000 mg/kg bw, 5/sex	LD_{50} > 5000 mg/kg bw Low Toxicity	1/5 ♂, 1/5 ♀ died Signs of decreased activity, hunched posture, piloerection, ungroomed condition, and ataxia Decedents showed gasping, hair loss, pigmented staining of snout One of each sex had dark punctate foci on the thymus
Dermal	98.5%, CD rats, 2 g/kg bw, 5/sex	LD_{50} > 2000 mg/kg bw Low Toxicity	No mortality, no clinical signs One male had a slightly enlarged cervical lymph node
Inhalation	98.5%, SD rats, 0.309, 0.407, 5.32, and 0.684 mg/L, 10/sex/dose	LC_{50} ♂ = 0.463 mg/L ♀ = 0.476 mg/L Moderate Toxicity	0.309 mg/L – 4/10 ♂, 1/10 ♀ died 0.407 mg/L – 4/10 ♂, 4/10 ♀ died 0.532 mg/L – 7/10 ♂, 5/10 ♀ died 0.684 mg/L – 5/10 ♂, 9/10 ♀ died Signs of decreased activity and respiratory rate, cloudy eyes, gasping, and abnormal breathing sounds All treated rats showed significant weight loss, but recovered by day 14 Both sexes showed hyperemia and hemorrhage in the lungs and white foam in the trachea **WARNING—POISON.**
Skin Irritation	97.9%, NZW rabbits, 0.5 g, 3/sex	Mean 24/48/72 h = 0.8/8.0	Slight irritant

STUDY and MRID	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL mg/kg bw/day	TARGET ORGAN/SIGNIFICANT EFFECTS/ COMMENTS
Eye Irritation	97.9%, NZW rabbits, 0.1mL, 3/sex	Mean 24/48/72 h = 28.9/110, persistence of corneal opacity through 21 days.	Extreme irritant. **DANGER—CORROSIVE TO EYES.**
Skin Sensitization (Modified Buehler)	100%, Hartley guinea pigs, 0.4 mL/animal, 20/sex in test group, 10/sex in each control group, vehicle 80% ethanol in deionized water, induction and challenge at 100% a.i.	Control—2/10 very slight erythema. Test—8/20 very slight erythema.	Non-sensitizer.
Skin Sensitization (Modified Buehler)	96.7%, Hartley guinea pigs, 0.4 mL/animal, 20/sex in test group, 10/sex in each control group, vehicle propylene glycol, induction at 50% a.i., challenge at 30% a.i.	Control—2/10 very slight erythema. Test—5/20 very slight, 12/20 slight, 3/20 moderate erythema.	**Potential Skin Sensitizer.**
Allegro 500F Agricultural Fungicide—Acute toxicity data			
STUDY	**TEST MATERIAL; TEST SPECIES/STRAIN AND DOSES**	**LD_{50} mg/kg bw/day LC_{50} mg/L ACUTE TOX ENDPOINTS**	**TARGET ORGAN/SIGNIFICANT EFFECTS/ COMMENTS**
Note: All studies were conducted with a test material identified as Fluazinam 500F; the test material is chemically identical to Allegro 500F. Thus, the acute toxicity data are acceptable for the support of the registration application of Allegro 500F Agricultural Fungicide.			
Oral—rat	**Fluazinam 500F** rat, Sprague-Dawley ZML SD (MBM); 5/sex 5000 mg/kg bw	LD_{50} ♂♀ > 5000 mg/kg bw	mortality: no deaths clinical signs: soft feces and anogenital staining, ↓ activity, all normal by day 8 bw: all gained weight gross pathology: no abnormalities **Low toxicity**
Dermal—rabbit	**Fluazinam 500F** rabbit, New Zealand White; 5/sex 2000 mg/kg bw	LD_{50}, ♂♀ > 2000 mg/kg bw	no mortality, no effects on clinical signs, bw, or gross pathology at terminal sacrifice dermal effects: moderate to well-defined erythema, slight to moderate edema; desquamation; lasting for most of observation period **Low toxicity**
Inhalation—rat 4 h whole body exposure	**Fluazinam 500F** rat, Sprague-Dawley 5/sex/group 0, 2.64 mg/L (actual) 0, 25.6 mg/L (nominal)	MMAD = 5.2 µm, 66 and 36% aerosol particles <7 and 4 µm, respectively LC_{50}, ♂♀ > 2.64 mg/L	no mortality, no effects on bw and gross pathology clinical signs during exposure: moisture droplets on body fur post-exposure: orange staining fur **Low toxicity**
	Fluazinam 500F rat, Sprague-Dawley 5/sex/group 0, 1.03 mg/L (actual) 0, 23 mg/L (nominal)	MMAD = 10.2 µm, 31 and 7% aerosol particle <6 and 1 µm, respectively LC_{50}, ♂♀ > 1.03 mg/L	no mortality, no effects on gross pathology clinical signs during exposure: partial eye closure, ↑ salivation, exaggerated respiration post-exposure: noisy respiration, orange stained fur bw ↓ gain during week 1, normal thereafter **Low toxicity**
Eye irritation—rabbit	**Fluazinam 500F** rabbit, New Zealand White; 3/sex 0.1 mL	Maximum mean score at 24 h = 7.7/110	no corneal or iridal effects conjunctiva: redness, chemosis, and/or discharge mean irritation scores: at 1–2, 24, 48, 72 h, and d 4 = 7.3, 7.7, 6.0, 1.7, and 0 (maximum = 110), respectively **Minimally irritating**

STUDY	TEST MATERIAL; TEST SPECIES/STRAIN AND DOSES	LD_{50} mg/kg bw/day LC_{50} mg/L ACUTE TOX ENDPOINTS	TARGET ORGAN/SIGNIFICANT EFFECTS/ COMMENTS
Skin irritation (4 h)—rabbit	**Fluazinam 500F** rabbit, New Zealand White; 3/sex 0.5 mL	Maximum mean score = 5.0/8 at 24/48 h; primary irritation index = 4.5/8	skin reaction: well-defined to moderate erythema very slight to slight edema; desquamation mean irritation scores (maximum = 8) at 0.5, 1, 24, 48, 72 h and d 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14—3.9, 5.0, 5.0, 4.0, 2.2, 2.2, 2.0, 1.8, 2.0, 2.0, 2.0, 2.0, 1.5, 2.0, 2.0, respectively **Moderately irritating** **WARNING—SKIN IRRITANT**
Dermal sensitization—guinea pig (Buehler test)	**Fluazinam 500F** guinea pig, Hartley, 10/sex/group test, naive, positive	induction: 3, 1/wk with undiluted formulation challenge: 1, with 30% aqueous preparation	inductions: progressively more severe reaction after successive induction applications challenge: more test animals responded; response was more pronounced in test animals **Potential skin sensitizer**
SHORT TERM			
4-week dietary	96.3%, CD/SD rats, 0, 10, 50, 250, 3000 ppm, 10/sex/dose (0, 1.0, 5.1, 26.4, 302 mg/kg/d ♂; 0, 1.1, 5.3, 25.9, 309 ♀)	NOAEL 50 ppm (5.1 mg/kg/d in males and 5.3 in females) LOAEL 250 ppm (26.4 mg/kg/d in males and 25.9 in females)	250 ppm ↓ bwg, food consumption ♀ ↑ total cholesterol, rel liver weight ♀ ↑ total cholesterol, periacinar hypertrophy ♂ 3000 ppm ↓ bwg, food consumption ♂ and ♀ ↑ serum phospholipid, total cholesterol, abs and rel liver weights ♂ and ♀ ↑ single cell necrosis ♀ ↑ periacinar hypertrophy ♂
90-day dietary	98.5%, SD rats, 0, 2, 10, 50, 500 ppm, 10/sex/dose (0, 0.15, 0.77, 3.8, 38 mg/kg/d ♂; 0, 0.17, 0.86, 4.3, 44 ♀)	NOAEL 50 ppm (3.8 mg/kg/d in males and 4.3 in females) LOAEL 500 ppm (38 and 44 mg/kg/d)	↑ relative liver weight ♂ (within hist cntrl) ↑ absolute lung weight ♀ (within hist cntrl); relative lung weight ↑ 25% ↑ abs and rel uterus weight ♀ ↑ periacinar hepatocyte hypertrophy and sinusoidal chronic inflammation ♂
90-day dietary non-guideline	98.5%, CD rats, 0, 500 ppm, 10/sex/dose. Another 10/sex/dose given same before a 4-week recovery phase	LOAEL 500 ppm (37.6 mg/kg/d in males and 44.7 in females)	↑ relative liver weight during feeding phase (12% ♂, 15% ♀) and periacinar hypertrophy in all males. These effects were reversible after 4 weeks of non-dosing
90-day dietary	98.5%, Beagles, 0, 1, 10, 100 mg/kg/d, 4/sex/dose	NOAEL 10 mg/kg/d LOAEL 100 mg/kg/d	Retinal effects (slight hyper-reflection, mottling of tapetal fundus) ♂♀ ↑ Serum plasma alk phos levels ♀ ↑ abs and rel liver weight ♂♀ Hepatic coagulative necrosis ♂♀ Slight to moderate bile duct hyperplasia ♂♀ Possible ↑ in white matter vacuolation graded trace in 1 ♂, 2 ♀
11-week dietary for eye effects	98.0% and 98.1%, Beagles, 0, 200/150 mg/kg bw/d, 6 males/dose	LOAEL 200/150 mg/kg/d (5/6 wks resp.)	Loose/liquid feces, vomiting, inappetance, excess salivation, vasodilation ↓ body weights (17%) Effects on eyes in previous study were not repeated. Brown granularity of the tapetal fundus was seen in two treated animals, but only to a very slight degree

STUDY	TEST MATERIAL; TEST SPECIES/STRAIN AND DOSES	LD_{50} mg/kg bw/day LC_{50} mg/L ACUTE TOX ENDPOINTS	TARGET ORGAN/SIGNIFICANT EFFECTS/ COMMENTS
21-day dermal	98.0%, CD rats, 0, 10, 100, 1000 mg/kg/d, 10/sex/dose	NOAEL 100 mg/kg/d LOAEL 1000 mg/kg/d	1000 mg/kg/d ↓ bwg ♂ (19%) ↑ Abs liver weight ♂♀ (17–26%), rel liver weight (27–30%), AST and cholesterol, periacinar hepatocellular hypertrophy Acanthosis, dermatitis, scabs, and ulceration were noted in ♂♀ 100 mg/kg/d ↑ AST and cholesterol ♂—Not considered adverse
CHRONIC TOXICITY/ONCOGENICITY			
Oral 2 year	95.3%, Crj:CD(SD)BR rats, 0, 25, 50, 100 ppm, 25/sex/dose (0, 1.0, 1.9, 3.9 mg/kg/d ♂, 0, 1.2, 2.4, 4.9 ♀)	NOAEL 100 ppm (4.9 mg/kg/d for females), 50 ppm (1.9 mg/kg/d for males) LOAEL 100 ppm (3.9 mg/kg/d for males), >100 ppm (4.9 mg/kg/d for females)	100 ppm Transient ↑ in cholesterol at week 52 and relative liver weights without histopath at study end in ♀ ↑ incidence of small and/or flaccid testes in decedents (same incidence when survivors are included, but severity is worse at high dose). Histopath showed tubular atrophy. These effects were seen in other studies. No treatment-related ↑ in tumours
Carcinogenicity 2 year	95.3%, CD-1 mice, 0, 1, 10, 100, 1000 ppm, 52/sex/dose (0, 0.12, 1.1, 10.7, 107 mg/kg/d ♂, 0, 0.11, 1.2, 11.7, 117 ♀)	NOAEL 10 ppm (1.1 mg/kg bw/d for males, 1.2 for females) LOAEL 100 ppm (10.7 mg/kg/d for males, 11.7 for females) Positive for hepatocellular adenomas, carcinomas, combined adenoma/carcinoma in males at 107 mg/kg/d	100 ppm ↑ incidence of brown pigmented macrophages in livers ♂ and ♀ ↑ incidence of eosinophilic vacuolated hepatocytes ♂ ↑ adj liver weights ♀ 1000 ppm ↑ adj liver weights (45% ♂, 30% ♀) ↑ basophilic or eosinophilic vacuolated hepatocytes ♂ ↑ granulomatous hepatitis of minimal severity, aggregates of brown pigmented macrophages in livers ♂ and ♀ ↑ thymic hyperplasia ♀ ↑ cystic thyroid follicles ♂ and ♀ ↑ incidence and severity of white matter vacuolation in brains ♂ and ♀

STUDY	TEST MATERIAL; TEST SPECIES/STRAIN AND DOSES	LD_{50} mg/kg bw/day LC_{50} mg/L ACUTE TOX ENDPOINTS	TARGET ORGAN/SIGNIFICANT EFFECTS/ COMMENTS
Carcinogenicity 2 year	97.0%, CD-1 mice, 0, 1000, 3000, 7000 ppm, 50 mice/sex/dose (0, 126, 377, 964 mg/kg/d ♂; 0, 162, 453, 1185 ♀)	NOAEL < 1000 ppm LOAEL 1000 ppm (126 mg/kg/d for males, 162 for females) Negative for dose-related trends for hepatocellular adenomas, carcinomas, combined adenoma/carcinoma in males, but there was a statistically significant increase in hepatocellular adenomas and combined adenoma/carcinoma in mid-dose males. High-dose males had increased incidences in these endpoints over controls, but less than mid-dose and within historical controls. Females had a statistically significant positive trend for combined hepatocellular adenomas/carcinomas, but only when including the toxicologically excessive 7000 ppm dose	≥1000 ppm ↑ rel liver weights (54% ♂, 21% ♀) ↑ incidence of altered hepatocyte foci ♂ ↑ incidence and/or severity of hepatocyte enlargement, pale or vacuolated hepatocyte cytoplasm, and brown pigmented macrophage aggregates ♂ and ♀ ↑ incidence and severity of white matter vacuolation in brains ♂ and ♀ 3000 ppm ↑ rel liver weights (113% ♂, 45% ♀) 7000 ppm ↓ survival ♀, all terminated at 97 weeks due to low survival ↓ bwg, food efficiency ♂ ↑ rel liver weights (182% ♂, 109% ♀) ↑ incidence of altered hepatocyte foci ♀ ↑ incidence of left atrial thrombus contributing to 46 and 30% of deaths ♂ and ♀ respectively
Carcinogenicity 2 year	95.3%, SD rats, 0, 1, 10, 100, 1000 ppm, 60/sex/dose (0, 0.04, 0.38, 3.8, 40 mg/kg/d ♂; 0, 0.05, 0.47, 4.9, 53 ♀)	NOAEL 10 ppm (0.38 mg/kg/d for males, 0.47 for females) LOAEL 100 ppm (3.8 mg/kg/d for males, 4.9 for females) Positive for thyroid gland follicular cell adenocarcinomas and combined follicular cell adenomas/adenocarcinomas in males at 40 mg/kg/d	100 ppm Numerous liver lesions in ♂ and ♀ Pancreatic exocrine atrophy ♀ Testicular atrophy ♂ 1000 ppm Straw-discolouration of fur ♂ and ♀ ↑ incidence of alopecia ♀ ↑ mild anemia and elevated cholesterol ♂ and ♀ ↓ bwg, food efficiency ♂ and ♀ ↑ abs and rel liver weights ♂ and ♀ ↑ Numerous liver lesions ♂ and ♀ ↑ Centrilobular fat and bile duct hyperplasia ♂ and ♀ ↑ Acinal epithelial vacuolation or fat accumulation ♀ ↑ Exocrine degranulation at interim ♀ ↑ Thyroid follicular hyperplasia ♂ and ♀ ↑ Cortical tubular basophilia in the kidney ♂ ↑ Pneumonitis, alveolar adenomatosis, and alveolar epithelialization ♂ ↑ Alveolar epithelialization and alveolar macrophage aggregates ♀ ↑ Testicular atrophy ♂ ↑ Sinus histiocytosis in lymph nodes ♀

STUDY	TEST MATERIAL; TEST SPECIES/STRAIN AND DOSES	LD_{50} mg/kg bw/day LC_{50} mg/L ACUTE TOX ENDPOINTS	TARGET ORGAN/SIGNIFICANT EFFECTS/ COMMENTS
Oral 1 year	95.3%. Beagles. 0. 1. 10. 50 mg/kg/d. 6/sex/dose	NOAEL 1 mg/kg/d LOAEL 10 mg/kg/d	10 mg/kg/d ↑ Nasal dryness ♀ ↑ Incidence and severity of gastric lymphoid hyperplasia ↓ Myeloid to erythroid ratios in bone ♀ 50 mg/kg/d ↑ Nasal dryness and salivation ♂ and ♀ ↓ bwg in both sexes, but only significant in ♀ ↓ Myeloid to erythroid ratios in bone ♀ ↓ Hematocrit, hemoglobin, RBC ♂ and ♀ ↑ WBC mid and high doses ♂ and ♀ ↑ Alk phos, cholesterol ♂ and ♀ ↑ Abs and rel liver weight ♂ and ♀ ↑ Incidence and severity of white matter vacuolation in brain ♂ and ♀ and spinal cord ♀ ↑ Incidence and severity of gastric lymphoid hyperplasia
REPRODUCTION/DEVELOPMENTAL TOXICITY			
Multi-generation	95.3%. SD rats. 0. 20. 100. 500 ppm. 24/sex/dose F_0 (0. 1.5. 7.3. 36.6 mg/kg/d ♂; 0. 1.7. 8.4. 42.1 ♀) F_1 (0. 1.9. 9.7. 47.3 mg/kg/d ♂; 0. 2.2. 10.6. 53.6 ♀)	Developmental NOAEL 100 ppm (8.4 mg/kg/d. F_1 ♀) Developmental LOAEL 500 ppm (42.1 mg/kg/d. F_1 ♀) Reproductive NOAEL 100 ppm (10.6 mg/kg/d. F_1 ♀) Reproductive LOAEL 500 ppm (53.6 mg/kg/d. F_1 ♀) Parental NOAEL 20 ppm (1.9 mg/kg/d. F_1 ♂) Parental LOAEL 100 ppm (9.7 mg/kg/d. F_1 ♂)	100 ppm ↑ Periacinar hepatocytic fatty changes F_1 ♂ 500 ppm ↓ bwg, food consumption F_1 ♀, F_1 ♂ and ♀ ↑ Rel liver weight F_1 ♂ and ♀, F_2 ♀ ↑ Periacinar hepatocytic fatty changes F_1, F_2 ♂ ↓ Hepatic glycogen pallor F_1 ♂ ↓ Implantation sites F_1 dams ↓ Mean litter size F_1 litters ↓ bwg during lactation F_1 and F_2 pups ↓ Time for pinna unfolding, hair growth, eye opening (all slight) F_2 pups
Developmental	98.5%. NZW Rabbits. 0, 2, 4, 7, 12 mg/kg/d. 16–18 pregnant females/dose	Maternal NOAEL 4 mg/kg/d Maternal LOAEL 7 mg/kg/d Developmental NOAEL 7 mg/kg/d Developmental LOAEL 12 mg/kg/d Qualitative sensitivity of young	7 mg/kg/d ↓ Food consumption ↑ Liver histopath (cellular hypertrophy, single cell necrosis, binucleate hepatocytes, brown pigment deposition, apoptosis) 12 mg/kg/d ↓ bwg, food consumption ↑ Liver histopath (cellular hypertrophy, single cell necrosis, binucleate hepatocytes, brown pigment deposition, apoptosis) ↑ Incidence total litter resorptions ↑ Incidence placental anomalies ↑ Skeletal abnormalities (slight) (kinked tail tip, fused or incompletely ossified sternebrae, abnormalities of head bones)
Developmental	98.5%. CD/SD rats. 0, 1, 10, 100, 1000 mg/kg bw, 7 pregnant females/dose	Range finding study	100 mg/kg/d ↑ Incomplete ossification of sternebrae ↑ Litters with fetuses and percentage of fetuses with additional (14th) rib(s) (slight) 1000 mg/kg/d Excessive maternal toxicity

STUDY	TEST MATERIAL; TEST SPECIES/STRAIN AND DOSES	LD_{50} mg/kg bw/day LC_{50} mg/L ACUTE TOX ENDPOINTS	TARGET ORGAN/SIGNIFICANT EFFECTS/ COMMENTS
Developmental	98.5%, CD/SD rats, 0, 10, 50, 250 mg/kg bw, 20 pregnant females/dose	Maternal NOAEL 50 mg/kg/d Maternal LOAEL 250 mg/kg/d Developmental NOAEL 50 mg/kg/d Developmental LOAEL 250 mg/kg/d Qualitative sensitivity of young. Teratogenic at maternally toxic doses.	250 mg/kg/d ↓ bwg, food consumption. ↑ Water consumption. ↑ Urogenital staining. ↓ Fetal BW, placental weights. ↑ Incidence of facial/palate clefts, diaphragmatic hernia, delayed ossification in several bone types, greenish amniotic fluid, possible late resorption/postimplantation loss.
GENOTOXICITY			
Ames mutagenicity test	TA1535, 100, 1537, 98, *E. coli* WP2 uvrA, with and without S9	Negative	
Ames mutagenicity test	TA1535, 100, 1537, 98, *E. coli* WP2 uvrA, with and without S9	Negative	
CHO/HPRT mutagenicity test	With and without S9	Negative	
In vivo cytogenetics chromosome aberration in mouse bone marrow	Without S9	Negative	
Differential growth inhibition	With and without S9	Negative	
NEUROTOXICITY			
Acute	96.8%, SD rats, 0, 50, 1000, 2000 mg/kg bw, 10/sex/dose, gavage	NOAEL 2000 mg/kg (Neurotox) LOAEL >2000 mg/kg (Neurotox) NOAEL 50 mg/kg (Systemic) LOAEL 1000 mg/kg (Systemic)	Soft stools ♀ at 1000 and 2000 mg/kg had ↓ mean motor activity on day of dosing (non-dose-related, not seen in subchronic)
Subchronic 90 day	96.9% Crl:CD BR rats, 0, 300, 1000, 2000, 3000 ppm, 10/sex/dose (0, 20.7, 69–74, 149, 233 mg/kg/d ♂; 0, 23.4, 81–89, 175, 280 ♀)	NOAEL 3000 ppm (233 and 280 mg/kg/d for ♂ and ♀) (Neurotox) LOAEL > 3000 (Neurotox) NOAEL 300 ppm (20.7 mg/kg/d ♀), 1000 ppm (69–74 mg/kg/d ♂) (Systemic) LOAEL 1000 ppm (81–89 mg/kg/d ♀), 2000 ppm (149 mg/kg/d ♂) (Systemic)	1000 ppm ♀ ↓ bwg 2000 and 3000 ppm ♂ and ♀ ↓ bwg, food consumption. 3000 ppm ♂ ↓ food efficiency. 300 ppm and up ♀ ↓ food efficiency (dose related)

STUDY	TEST MATERIAL; TEST SPECIES/STRAIN AND DOSES	LD_{50} mg/kg bw/day LC_{50} mg/L ACUTE TOX ENDPOINTS	TARGET ORGAN/SIGNIFICANT EFFECTS/ COMMENTS
SPECIAL/IMPURITIES			
Comparative—susceptibility to neurotoxicity	97.0% Impurity-5, 2.0 mg/kg/d, 5 Crj:CD (ICR) mice, 5 Crj:CD (SD) rats, 3 beagles, all male		↓ Spontaneous motor activity in rats and mice ↓ Mean body weight in mice and rats ↑ Brain weights in mice and rats Vacuolation of white matter and swelling of the brain in all treated animals. Dogs appear to be slightly less susceptible
Comparative—brain sensitivity rats and mice	99.5% Impurity-5, 0, 0.5 mg/kg, 5 Crj:CD-1 mice, 5 Crj:CD(SD) SPF/VAF rats, all female		Incidence and severity of white matter vacuolation in brains of mice and rats were similar. Brain weights were comparable to controls
Comparative—brain sensitivity 3- and 10-week old rats and mice—14 days	99.5% Impurity-5, 0, 0.5 mg/kg/d, 10 Crj:CD-1 (ICR) SPF/VAF mice and Crj:CD(SD) SPF/VAF rats, all male, half 3 weeks old, the other half 10 weeks old		Edema in brains of 1 rat and 2 mice (10 weeks old) Vacuolation in white matter of brains similar between species of same age, but more severe in older animals compared to younger
Effect on brain/optic nerves	99.5% Impurity-5, 2.5 mg/kg, Crj:CD-1(ICR) mice, 5 males/group, aged 3, 5, 8, 10, 12, 16, 20, 24 weeks		All treated mice except 3 week olds had vacuolation of the optic nerve. The effect was less severe than in the brain. The eyes themselves were normal <u>Ages 3, 5, 8 weeks</u> Trace vacuolation of white matter in brains <u>Ages 10, 12, 16, 20, 24 weeks</u> Trace to minimal vacuolation of white matter in brains
Various impurities—effect on brains	96–100% Impurities 1 through 9, doses correspond to 5000 mg/kg dose of technical, 5 male Crj:CD-1 mice (Impurity-5 was dosed at 5 mg/kg)		Only Impurity-5 was toxic Coarse fur, paralysis of hind legs, staggering gait, sedation, moribund ↓ Mean body weight ↑ Brain weight, edema Vacuolation of white matter
Comparing technical and analytical standard	97.0%, 95.3%, 99.7%, two-fold 3000 or one-fold 5000 mg/kg/d, 5 male Crj:CD-1 mice		<u>Technical</u> ↓ Motor activity Prone position, paralysis of hind legs, tremor, or staggering gait, moribund ↓ Mean body-weight gain ↑ Brain weight, edema Vacuolation of white matter Enlargement, accentuated lobular patterns, and pale discolouration of liver <u>Analytical</u> Occasional liver abnormalities similar to technical Fluazinam: No white matter vacuolation
Effect on brain—recovery	96.2%, 0, 10 000, 30 000 ppm, 7 male Crj:CD rats (0, 714, 1743 mg/kg/d)		1 found dead, two killed in extremis ↓ Motor activity and anemia in those died/killed ↑ Coarse fur in treated groups Emaciation in high dose ↓ Mean body weight, food consumption <u>Sacrificed after treatment</u> Edema in brains, enlarged and discoloured livers White matter vacuolation was trace at low dose and mild–moderate at high <u>25-day recovery</u> White matter vacuolation absent in low dose and trace at high

STUDY	TEST MATERIAL; TEST SPECIES/STRAIN AND DOSES	LD_{50} mg/kg bw/day LC_{50} mg/L ACUTE TOX ENDPOINTS	TARGET ORGAN/SIGNIFICANT EFFECTS/ COMMENTS
Effect on brain—recovery	96.2% Crj:CD-1 mice. 0, 7000, 20 000 ppm. 10/sex/dose for 4 or 28 days (high dose not treated for 28 days), recovery for 7, 14, 24, or 56 days (0, 1043–1173, 1871 mg/kg/d)		20 000 ppm Abnormal posture, fur, mobility, bizarre behaviour, # unsupported rears, hindlimb grip strength, and landing foot splay during day 4 FOB. These observations dissipated by day 7 or 14 of recovery. ↓ Food consumption, recovery in first week. 7000 ppm, 4 d Vacuolation of white matter in brains not observed after 24 days recovery. 7000 ppm, 28 d and 20000 ppm, 4 d ↓ Mean body weight, bwg. Recovery occurred by day 14 Trace edema in brains and enlarged livers with accentuated lobular patterns and pale discolouration in mice sacrificed after treatment Vacuolation of white matter in brains not observed after 56 days recovery

Recommended ARfD

General population

0.013 mg/kg bw/d based on rabbit developmental (4 mg/kg/d with 100-fold uncertainty factor and three-fold safety factor (SF) for endocrine effects).

Females 13+

0.007 mg/kg bw/d based on rabbit developmental (7 mg/kg/d with 100-fold UF, three-fold SF for endocrine-related effects, and three-fold for lack of DNT).

Recommended ADI

0.0011 mg/kg bw/d based on 2 year carcinogenicity in mice (1.1 mg/kg/d with 100-fold UF, three-fold SF for endocrine-related effects (testicular atrophy, pancreatic exocrine atrophy ♀), and three-fold for lack of DNT).

MOS for other critical endpoint(s)

White matter vacuolation/Neurotox

NOEL for white matter vacuolation was 10 mg/kg/d in chronic dog study (equivalent to 0.02 mg/kg/d Impurity-5). MOS = 9100

Tumours

NOEL for tumours was 3.8 mg/kg bw/d in 2-year rat study. MOS = 3450

Developmental effects

NOAEL for developmental effects was 7 mg/kg bw/d in developmental rabbit study. MOS = 6350

Table 5 Food residue chemistry overview of metabolism studies and risk assessment

Direction for Use						
Crop	**Formulation Type**	**Interval (days)**	**Rate (g a.i./ha)**	**Application/ season**	**Maximum rate kg a.i./ha**	**PHI (days)**
Potatoes	SC	7 to 10	200	10	2	14

Physicochemical Properties	
Water solubility at 25°C (mg/L)	pH 5 (0.131); pH 7 (0.157); pH 9 (3.384)
Solvent solubility at 25°C (g/L)	acetone (853); dichloromethane (675); ethyl acetate (722); ethyl ether (231); hexane (8); methanol (192); octanol (41); toluene (451)
Octanol–water partition coefficient (Log K_{ow}) at 25°C	4.03
Dissociation constant (pKa) at 20°C	7.22 in 50% ethanol/water (v/v)
Vapour pressure (Pa)	25°C (2.3×10^{-5}); 35°C (1.3×10^{-4}); 45°C (6.7×10^{-4})
Relative density at 25°C (g/mL)	1.02
Melting point °C	Completed melted at 119°C
UV/Visible absorption spectrum	pH: 2; 7; >10 — Mean λmax: 238; 239, 342; 260, 343, 482 — Mean log ε: 4.31; 4.27, 3.86; 4.22, 4.27, 3.54

Analytical Methodology	
Parameters	**Plant matrices**
Method ID	Ganse, Y., (1991). Analytical methods for fluazinam and its metabolites in crops—revised method. Report Number F-154.
Type	Data gathering and enforcement (some modification to improve peak shape and minimize interferences from different plant matrices.
Analytes	Fluazinam, HYPA, MAPA
Instrumentation	Gas liquid chromatography with electron capture detector (ECD)
LOQ	0.01 ppm for each analyte.
Standard	An external standard method was used as marker for retention time, response and calibration.
ILV	The recovery results (70 to 120% obtained by an independent laboratory validated the enforcement method for the determination of fluazinam in potato matrices.
Extraction/clean-up	Extraction with methanol:acetic acid, followed by sequential partitioning with hexane and 0.2N HCl and 0.5N NaOH. Clean-up on a Florisil column.
Multiresidue method	Fluazinam was tested through the United States Food and Drug Administration Multiresidue Protocols (PAM Volume 1, Appendix II, I/94). Fluazinam was poorly recovered from grapes and peanut nutmeats. Therefore, the MRM cannot serve as an enforcement method.

Nature of the Residue in Potatoes				
Radiolabel	C-Nitrophenyl-^{14}C		2, 6-Pyridine-^{14}C	
Test Site	In field		In field	
Treatment	Foliar treatment		Foliar treatment	
Rate	4 applications × 0.5 kg a.i./ha for a total of 2.02 kg a.i./ha		4 applications × 0.43 kg a.i./ha for a total of 1.72 kg a.i./ha	
EP	Fluazinam as a suspension in water with the inert formulation ingredients			
PHI	6 to 7 days after the last application.			
Approximately 85 to 90% of the radioactivity entered the carbon pool and was reincorporated into natural products, or as highly polar degraded fragments of the parent molecule. See FIGURE 4.1.1.				
Metabolites identified	**Major metabolites (>10% TRRs)**		**Minor metabolites (<10% TRRs)**	
Radiolabel	**C-Nitrophenyl-^{14}C**	**2, 6-Pyridine-^{14}C**	**C-Nitrophenyl-^{14}C**	**2, 6-Pyridine-^{14}C**
Whole potato	Starch	Starch	Fluazinam, TFA, AMGT, AMPA	Fluazinam, TFA, AMGT, AMPA
Confined Rotational Crop Study—Lettuce, Carrot, Barley				
Radiolabels	C-Nitrophenyl-^{14}C and 2, 6-^{14}C-Pyridine			
Test Site	Madera, California			
Treatment	Application to bare soil (sandy loam), with lettuce, carrot and barley planted at 30, 120 and 365 DAT.			
Rate	2 broadcast applications of 1.12 kg a.i./ha, for a total of 2.24 kg a.i./ha			
EP	Methanol solutions			
PHI	Crops harvested at an intermediate stage of development and at maturity			
For the C-Nitrophenyl-^{14}C label, the major metabolite identified in all crops at all plantback intervals was trifluoroacetic acid (TFA). The 2, 6-Pyridine-^{14}C label yielded components produced by extensive metabolism of the pyridine ring, including ring opening and fragmentation for all crops at all plantback intervals. Additional analyses of the 2, 6-Pyridine-^{14}C labelled fluazinam demonstrated that a considerable amount of the radioactivity was recovered in natural products such as starch. Fluazinam was not identified in lettuce, carrot or barley grain, forage or straw.				
Nature of the Residue in Lactating Goat				
Species	**Radiolabel**		**Dose Level**	**Sacrifice**
Goat (*Alpine, Toggenburg*)	C-nitrophenyl-^{14}C and 2, 6-Pyridine-^{14}C		13.4 ppm (nitrophenyl) and 9.14 ppm (pyridine) for 4 consecutive days	23 h after last dose
For the C-Nitrophenyl-^{14}C label, 0.9% of the administered dose was in the tissues; 0.3% in milk; 8.9% in urine; 66% in feces; 9.9% in GI tract content; 0.08% in bile and < 0.01% in blood. For the 2, 6-Pyridine-^{14}C label, 1.6% of the administered dose was in the tissues; 0.6% in milk; 11.6% in urine; 62% in feces; 11% in GI tract content; 0.16% in bile and < 0.01% in blood. See FIGURE 4.1.2.1.				

Metabolites identified	Major metabolites (>10% TRRs)		Minor metabolites (<10% TRRs)	
Radiolabel	**C-nitrophenyl-^{14}C**	**2, 6-Pyridine-^{14}C**	**C-nitrophenyl-^{14}C**	**2, 6-Pyridine-^{14}C**
Liver	DAPA	—	DAPA sulfamate, AMPA	DAPA sulfamate, AMPA sulfamate, DAPA, AMPA
Kidney	DAPA, AMPA sulfamate	AMPA sulfamate	DAPA sulfamate, AMPA	DAPA sulfamate, AMPA, DAPA
Fat	DAPA, AMPA	DAPA, AMPA	—	—
Muscle	DAPA, AMPA	DAPA, AMPA	—	—
Milk	AMPA sulfamate, AMPA, DAPA	AMPA sulfamate, AMPA, DAPA	DAPA sulfamate	DAPA sulfamate
Urine	DAPA sulfamate	DAPA sulfamate	DAPA	DAPA
Bile	DAPA sulfamate	DAPA sulfamate, AMPA sulfamate, DAPA	AMPA sulfamate, DAPA	—

Nature of the Residue in Laying Hen

Species	Radiolabel	Dose Level	Sacrifice
Laying Hen *(Gallus domesticus)*	C-Nitrophenyl-^{14}C and 2, 6-Pyridine-^{14}C	Single dose at 10 ppm for 4 consecutive days (both labels)	6 hours after last dose

For the C-Nitrophenyl-^{14}C label, 101% of the administered dose was in the excreta, 11.1% in the GI tract contents, 2.24% in tissues, 0.14% in blood and 0.56% in eggs. For the 2, 6-Pyridine-^{14}C label, 99.1% of the administered dose was in the excreta, 11.9% in GI tract contents, 2.18% in tissues, 0.14% in blood and 0.38% in eggs. See FIGURE 4.1.2.2

Metabolites identified	Major metabolites (>10% TRRs)		Minor metabolites (<10% TRRs)	
Radiolabel	**C-nitrophenyl-^{14}C**	**2, 6-Pyridine-^{14}C**	**C-nitrophenyl-^{14}C**	**2, 6-Pyridine-^{14}C**
muscle, fat, kidney, liver, egg white	AMPA	AMPA	Fluazinam, MAPA, DAPA, HYPA	Fluazinam, MAPA, DAPA, HYPA
egg yolk	—	AMPA	Fluazinam, MAPA, DAPA, HYPA, AMPA	Fluazinam, MAPA, DAPA, HYPA

Crop Field Trials—Potatoes

Nineteen trials were conducted in U.S./Canada Zones 1, 1A, 5, 5A, 9, 10 and 11 over the course of 3 years (1992, 1993, 1994). Trials were 50 to 115% of the recommended label rate. Trials were under-represented in Canada's growing region (1A, 5B, 7A, 12, 14). It should be noted that the supervised residue trials were conducted prior to the publication of the Residue Chemistry Guidelines (DIR98-02).

Commodity	Rate kg a.i./ha	PHI (days)	Analyte	Residue Levels (ppm)					
				n	Min.	Max.	HAFT	Mean	SD
Potatoes	2 × 0.5	14	Fluazinam	2	< 0.01	< 0.01	< 0.01	NA	NA
Potatoes	3 × 0.5	14, 32, 34	Fluazinam	6	< 0.01	< 0.01	< 0.01	NA	NA
Potatoes	4 × 0.5	8, 14, 40	Fluazinam	8	< 0.01	< 0.01	< 0.01	NA	NA

Commodity	Rate kg a.i./ha	PHI (days)	Analyte	Residue Levels (ppm)					
				n	Min.	Max.	HAFT	Mean	SD
Potatoes	5 × 0.2	14	Fluazinam	2	< 0.01	< 0.01	< 0.01	NA	NA
Potatoes	7 × 0.2	14	Fluazinam	2	< 0.01	< 0.01	< 0.01	NA	NA
Potatoes	8 × 0.2	13, 14, 18	Fluazinam	10	< 0.01	< 0.01	< 0.01	NA	NA
Potatoes	9 × 0.2	14	Fluazinam	2	< 0.01	< 0.01	< 0.01	NA	NA
Potatoes	10 × 0.2	14	Fluazinam	4	< 0.01	< 0.01	< 0.01	NA	NA
Potatoes	11 × 0.2	14	Fluazinam	2	< 0.01	< 0.01	< 0.01	NA	NA

Residue Decline

Eight trials conducted in 1989–1990 in Germany at PHIs of 0, 6, 7, 13 and 14 days. Trials were 80 to 100% of the recommended label rate.

Commodity	Rate kg a.i./ha	PHI (days)	Analyte	Residue Levels (ppm)					
				n	Min.	Max.	HAFT	Mean	SD
Potatoes	8 × 0.2	0, 6, 7, 13, 14	Fluazinam	9	< 0.01	< 0.01	< 0.01	NA	NA
Potatoes	9 × 0.2	0, 7, 14	Fluazinam	5	< 0.01	< 0.01	< 0.01	NA	NA
Potatoes	10 × 0.2	0, 7, 14	Fluazinam	7	< 0.01	< 0.01	< 0.01	NA	NA

Maximum Residue Limits

Potatoes	0.02 ppm

Processing Studies

The processing study was conducted with potatoes treated at 2.9-fold the recommended label rate.

Fraction	Mean residue levels (ppm)	Calculated Concentration factor
Whole potatoes	< 0.01	—
Wet peels	< 0.01	0
Dry peels	< 0.01	0
Granules	< 0.01	0
Chips	< 0.01	0
French fries	< 0.01	0
Potato flakes	< 0.01	0

Livestock Feeding

Based on the lactating goat and poultry metabolism studies conducted at exaggerated rates in comparison to the maximum theoretical dietary burden (MTDB of 0.05 ppm), and the anticipated dietary burden calculations, no finite residues of fluazinam are expected in the livestock tissues and milk. A feeding study is not required.

Storage Stability

Fluazinam residues degraded but were still recoverable (78–90%) under freezer storage at –20 C in whole potatoes (363 d), potato wet peel (182 d), potato chips (1149 d), and potato granules (57 d). These periods covered the interval between storage and analysis from the supervised residue trials and metabolism trials. However, samples of potato granules and wet peel were stored up to 407 months (34% decline) and 347 months (49% decline), respectively.

Table 6 Overview of metabolism studies and risk assessment

Plant Studies			
ROC for Enforcement and Risk Assessment—Potatoes		Fluazinam The submitted potato metabolism study is adequate for purposes of uses on root crops only. The results from this study are of limited use for extrapolating to the metabolism of [^{14}C]fluazinam in other types of crops. Extensive analysis of soluble ^{14}C-residues could not be conducted as total radioactive residues in potatoes were low (≤25 ppb), and plants were treated at only ~1-fold the proposed maximum seasonal rate. In addition, ^{14}C-residues in samples of foliage were not examined.	
Rotational crops		Fluazinam	
Metabolic Profile in Diverse Crops		Not applicable since petitioned use is for potatoes only	
Animal Studies—Lactating Goat, Laying Hen			
ROC for Enforcement and Risk Assessment		Fluazinam, AMPA and DAPA and their sulfamate conjugates. These metabolites were the major residues in most livestock matrices and were assumed to be of similar toxicity as the parent.	
Metabolic Profile in Animals		Similar	
Fat-Soluble Residue		YES	
DIETARY RISK from food and water			
Chronic Non-Cancer Dietary Risk **ADI = 0.0011 mg/kg bw/day** **EEC = 0.00077 mg/kg (chronic)**	**POPULATION**	**ESTIMATED RISK (% of ADI)**	
		Food (MRLs)	**Food + EEC**
	All infants < 1 year old	1.2	6
	Children 1 to 2 years	3.9	6.1
	Children 3 to 5 years	3.7	5.7
	Children 6 to 12 years	2.5	3.9
	Youth 13 to 19 years	1.8	2.9
	Adults 20 to 49 years	1.4	2.8
	Adults 50+ years	1.4	2.8
	Females 13 to 49 years	1.3	2.7
	Total Population	1.7	3.2

Acute Dietary Exposure Analysis, Deterministic, 95th percentile EEC = 0.01455 mg/kg	POPULATION	ESTIMATED RISK (% of ARD)	
		Food (MRLs)	Food + EEC
ARfD = 0.007 mg/kg bw (females 13+)	Females 13+	1	12.2
ARfD = 0.013 mg/kg bw	Total Population	0.6	6.1
Cancer Risk Assessment Q* = 0.054 EEC = 0.00077 mg/kg Intermediate Refinements	Population	Food (STMR)	Food (STMR + EEC)
	All infants < 1 year old	3.5×10^{-7}	3.2×10^{-6}
	Children 1 to 2 years	1.2×10^{-6}	2.5×10^{-6}
	Children 3 to 5 years	1.1×10^{-6}	2.3×10^{-6}
	Children 6 to 12 years	7.4×10^{-7}	1.6×10^{-6}
	Youth 13 to 19 years	5.3×10^{-7}	1.2×10^{-6}
	Adults 20 to 49 years	4.2×10^{-7}	1.2×10^{-6}
	Adults 50+ years	4.1×10^{-7}	1.3×10^{-6}
	Females 13 to 49 years	3.9×10^{-7}	1.2×10^{-6}
	Total Population	5.2×10^{-7}	1.4×10^{-6}

Table 7 Fate and behaviour of fluazinam in the aquatic and terrestrial environment

Fate process	Endpoint	Interpretation[a]
AQUATIC		
Hydrolysis	Stable to hydrolysis at pH 5 at 22°C. $T_{1/2}$: 42 d at pH 7 $T_{1/2}$: 5.6 d at pH 9	An important route of transformation under alkaline environmental conditions.
Phototransformation in water	DT_{50}: 2.5 d at 25°C and pH 5.	Important route of transformation.
Aerobic sediment/ water	Study 1. DT_{50}: 20 and 32 h Study 2. DT_{50}: 2.9 and 3.2 d	Non-persistent in aerobic water-sediment systems.
Anaerobic sediment/water	DT_{50}: < 1 day	Non-persistent in anaerobic water sediment systems.
Bioconcentration with bluegill sunfish	BCF in fillet: 5.8–348 from day 0.1 to 35 BCF in viscera: 84–1850 from day 0.1 to 35 BCF in fillet: 58–1220 from day 0.1 to 35	Expected to be depurated in its parent form within 21 days of exposure.

TERRESTRIAL		
Hydrolysis	Stable to hydrolysis at pH 5 at 22°C. $T_{1/2}$: 42 d at pH 7 $T_{1/2}$: 5.6 d at pH 9	An important route of transformation under alkaline environmental conditions.
Phototransformation in soil	DT_{50}: 22.2 d in sandy loam soil at 25°C	Not an important route of transformation.
Aerobic soil biotransformation	DT_{50}: 38 and 72 d at 20°C and 1 kg/ha in sandy loam DT_{50}: 120 and 150 d at 20°C and 5 kg/ha in sandy loam DT_{50}: 160 and 200 d at 10°C and 1 kg/ha in sandy loam DT_{50}: 152 and 200 d at 20°C and 1 kg/ha in loamy sand	Classified as slightly persistent to persistent depending on temperature, and soil type.
Anaerobic soil biotransformation	DT_{50}: 4.5 d at 1 kg/ha in sandy loam (no aerobic incubation) DT_{50}: 32 d at 10°C and 1 kg/ha in sandy loam (aerobic incubation)	Classified as non-persistent under anaerobic conditions and slightly persistent with aerobic pre incubation.
Adsorption/ desorption	Adsorption K_{oc}: 1705 to 2316 mL/g	Classified as of slight to low mobility in soil, and a potential for partitioning into sediment.
Aged column leaching	95% of applied radioactivity remained in the top 5 cm of soil.	Low potential to leach.
Field dissipation of Allegro 500F in cropped plots	Nova Scotia, Canada on potato crops in sandy loam DT_{50}: 95 d; DT_{90}: 315 d. Fluazinam not detected > 15 cm soil depth. Ontario, Canada on potato crops in silty loam DT_{50}: 81.5 d; DT_{90}: 270 d. Fluazinam not detected > 15 cm soil depth. Ephrata, Washington on bean plants in loamy sand DT_{50}: 19.8 d; DT_{90}: 340 d. Fluazinam not detected > 15 cm soil depth. Kempton, North Dakota on bean crops in sandy loam DT_{50}: 33 d; DT_{90}: 340 d. Fluazinam was detected in 15–30 cm soil depth at 3% of applied amount.	Slightly to moderately persistent. Low potential to leach in the soil profile.

Classification of persistence in soil according to Goring et al. (1975); classification of persistence in water according to McEwan and Stephenson (1979); classification of adsorption/desorption and mobility according to McCall et al. (1981).

Table 8 Fluazinam drinking water EECs

Crop and rate of application	Groundwater (µg a.i./L)		Surface Water			
			Reservoir (µg a.i./L)		Dugout (µg a.i./L)	
	Acute[1]	Chronic[2]	Acute[3]	Chronic[4]	Acute[3]	Chronic[4]
Potato	0	0	13.1	0.7	14.5	0.41

1 90th percentile of daily average concentrations
2 90th percentile of yearly average concentrations
3 90th percentile of yearly peaks
4 90th percentile of yearly averages

Table 9 The maximum EECs of fluazinam on vegetation and other food sources immediately following application at a rate of 2000 g a.i./ha[a]

Environmental Compartment	Concentration fresh weight (mg a.i./kg)a	Fresh weight/dry weight ratios	Concentration dry weight (mg a.i./kg)
short range grass	428.01	3.3	1412.43
leaves and leafy crops	223.99	11	2463.99
long grass	195.99	4.4	862.39
forage crops	240	5.4	1296
small insects	103.99	3.8	395.19
pods with seeds	21.4	3.9	83.46
large insects	17.8	3.8	67.64
grain and seeds	17.8	3.8	67.4
fruit	26.8	7.6	203.67

a Maximum application rate
b Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973)

Table 10 Summary of effects of fluazinam on terrestrial organisms

Organism	Exposure	Test Substance	Endpoint value	Degree of Toxicity[a]
Earthworm (*Eisenia foetida*)	28-day acute	fluazinam	LC_{50}: >1000 mg a.i./kg artificial substrate NOEC (mortality): 100 mg a.i./kg substrate NOEC (weight loss): 10 mg a.i./kg substrate LOEC (weight loss): 100 mg a.i./kg substrate	non-lethal > 100 mg a.i./kg substrate
Bee	48-hour acute contact	fluazinam	LD_{50}: > 200µg a.i./bee NOEC (mortality): 200 µg a.i./bee	non-toxic (Atkins et al. 1981)
	72-hour acute oral	fluazinam	LD_{50}: > 100 µg a.i./bee NOEC (mortality): 100 µg a.i./bee	non-toxic (Atkins et al. 1981)
Bobwhite quail (*Colinus virginianus*)	14-day acute oral	fluazinam	LD_{50}: 1782 mg a.i./kg bw **NOEL (mortality): 500 mg a.i./kg bw** NOEL (body weight): 1950 mg a.i./kg bw	moderately toxic
	8-day dietary	fluazinam	LC_{50}: >10 500 mg a.i./kg diet NOEC (mortality): 2480 mg a.i./kg diet *NOEC (body weight): 5230 mg a.i./kg diet	practically non-toxic
	22-week reproduction	fluazinam	NOEC (parental mortality): 750 mg a.i./kg diet NOEC (parental body weight): 1500 mg a.i./kg diet NOEC (parental food consumption): 750 mg a.i./kg diet) **NOEC (hatching success and 14-day survival): 500 mg a.i./kg diet**	
Mallard duck (*Anas platyrhynchos*)	14-day acute oral	fluazinam	LD_{50}: >4190 mg a.i./kg bw NOEL (mortality): 4190 mg a.i./kg bw NOEL (body weight): 4190 mg a.i./kg bw	practically non-toxic

Organism	Exposure	Test Substance	Endpoint value	Degree of Toxicity[a]
	8-day dietary	fluazinam	LC_{50}: >10 600 mg a.i./kg diet NOEC (mortality): 5230 mg a.i./kg diet NOEC (body weight)*: 5230 mg a.i./kg diet	practically non-toxic
	22-week reproduction	fluazinam	NOEC (parental mortality): 750 mg a.i./kg diet NOEC (parental body weight): 1000 mg a.i./kg diet NOEC (parental food consumption): 1000 mg a.i./kg diet) **NOEC (egg production, embryo viability, 14 d old survivorship): 500 mg a.i./kg diet**	—
Mammals				
Rats	Acute oral	fluazinam	LD_{50} >5000 mg/kg bw	low toxicity
	4-week dietary	fluazinam	NOAEL: 50 ppm 5.1 mg/kg/d ♂ 5.3 mg/kg/d ♀	—
	90-day dietary	fluazinam	NOAEL: 50 ppm 3.8 mg/kg/d ♂ 4.3 mg/kg/d ♀	—
	Reproduction	fluazinam	$NOAEL_{parental}$: 20 ppm (1.9 mg/kg/d, F_1 ♀) $NOAEL_{reproduction}$: 100 ppm (10.6 mg/kg/d, F_1 ♀) $NOAEL_{development}$: 100 ppm (8.4 mg/kg/d)	—
Dog	90-day dietary	fluazinam	NOAEL: 10 mg/kg/d	—
Vascular plants				
Vascular plants	Seed germination	fluazinam	EC_{25}: >1500 g a.i./ha. The most sensitive monocot was oats (3.8% inhibition) and the most sensitive dicot was cucumber (5.4% inhibition)	
	Seedling emergence	fluazinam	EC_{25}: >1500 g a.i./ha. The most sensitive monocot was sorghum (7% inhibition), the most sensitive dicot was tomato (12.7% inhibition)	

Organism	Exposure	Test Substance	Endpoint value	Degree of Toxicity[a]
	Fresh plant weight	fluazinam	EC_{25}: >1500 g a.i./ha. The most sensitive monocot was sorghum (5.3% inhibition), the most sensitive dicot was cucumber (1% inhibition)	
	Tier I Vegetative vigour plant fresh weight)	fluazinam	**Estimated EC_{25}: 1500 g a.i./ha (cucumber)** The most sensitive monocot was onion (9.8% inhibition) and the most sensitive dicot was cucumber (29.5% inhibition)	
	Tier II Vegetative vigour (plant fresh weight of cucumber)	fluazinam	EC_{25}: >1500 g a.i./ha. Weight inhibition was -26% (stimulatory)	

* NOEC based on day 5 data. All birds exhibited similar body-weight gain by day 8 (after treatment ended).

[a] Based on the classification scheme of USEPA (1985) unless otherwise stated.

Table 11 Summary of toxicity of fluazinam to aquatic organisms

Group	Organism	Exposure	Test substance	Endpoint	Degree of Toxicity[a]
Freshwater Invertebrates	*Daphnia magna*	acute 48 h (flow-through test)	fluazinam	**NOEC (mortality): 54 µg a.i./L** LC_{50}: 220 µg a.i./L	highly toxic
		acute 48 h (static)	fluazinam	NOEC (mortality): <55.5 µg a.i./L LC_{50}: 220 µg a.i./L *supplemental study*	highly toxic
		chronic 21 d	fluazinam	NOEC (parental mortality): 68 µg a.i./L LC_{50}: >140 µg a.i./L NOEC (reproduction): 140 µg a.i./L	—
Marine Invertebrates	Mysid shrimp (*Mysidopsis bahia*)	acute 96 h	fluazinam	NOEC (mortality): 13 µg a.i./L LC_{50}: 39 µg a.i./L	very highly toxic
	Eastern oyster (*Crassostrea virginica*)	acute 96 h	fluazinam	**NOEC (shell growth): 1.4 µg a.i./L** EC_{50}: 4 µg a.i./L	very highly toxic

Group	Organism	Exposure	Test substance	Endpoint	Degree of Toxicity[a]
Freshwater Fish	Rainbow trout* (*Onchorynchus mykiss*)	acute 96 h (hardness 50–56 mg/L $CaCO_3$)	fluazinam	NOEC (mortality): 64 µg a.i./L LC_{50}: 111 µg a.i./L	highly toxic
		acute 96 h (hardness 28–30 mg/L $CaCO_3$)	fluazinam	NOEC (mortality): 28 µg a.i./L LC_{50}: 36 µg a.i./L	very highly toxic
	Bluegill sunfish (*Lepomis macrochirus*)	acute 96 h	fluazinam	**NOEC (mortality): 21 µg a.i./L** LC_{50}: 55 µg a.i./L	very highly toxic
	Fathead minnow (*Pimephales promelas*)	34 d chronic (early life stage)	fluazinam	NOEC (hatching success): 10 µg a.i./L NOEC (fry mortality): 5.3 µg a.i./L	—
	Fathead minnow (*Pimephales promelas*)	278 d chronic (complete life-cycle	fluazinam	Most sensitive F_0 generation NOEC (reproduction**): 2.9 µg a.i./L **Most sensitive F_1 generation NOEC (hatching success): 0.69 µg a.i./L**	
Marine Fish	Sheepshead minnow (*Cyprinodon varigatus*)	acute 96 h	fluazinam	NOEC (mortality): 80 µg a.i./L LC_{50}: 120 µg a.i./L	highly toxic
Freshwater Vascular Plants	Duck weed (*Lemna gibba*)	7 d	fluazinam	EC_{50} (frond + biomass): >53.6 µg a.i./L NOEC (frond + biomass): 28.8 µg a.i./L	—

Group	Organism	Exposure	Test substance	Endpoint	Degree of Toxicity[a]
Freshwater algae	Green algae (*Selenastrum capricornutum*)	acute 96 h	fluazinam	EC_{50} (cell density): 180 µg a.i./L NOEC (cell density): 48 µg a.i./L **EC_{50} (biomass): 150 µg a.i./L** **NOEC (biomass): 48 µg a.i./L** EC_{50} (growth rate): >200 µg a.i./L NOEC (growth rate): 82 µg a.i./L	—

— No toxicity classification based on study type
* Results were presented for both studies since hardness affected the recovery of test material
** Spawn/female
[a] Based on the classification scheme of the USEPA (1985) unless otherwise stated

Table 12 Maximum EEC in diets of birds and mammals

Organism	Matrix	Fluazinam (mg a.i./kg dw diet)
Bobwhite quail	30% small insects 15% forage crops 55% grain	350.03
Mallard duck	30% large insects 70% grain	67.47
Rat	70% short grass 20% grain/seeds 10% large insects	1008.99
Mouse	25% short grass 50% grain/seeds 25% leaves and leafy crops	1002.93
Rabbit	25% short grass 25% leaves and leafy crops 25% long grass 25% forage crops	1508.71